# Parkinson's disease and impairments in executive functions

*Assessment and treatment from a neuropsychological perspective*

Thialda Teakje Hoogstins-Vlagsma

This research is funded by the Netherlands Initiative Brain and Cognition (NIHC), a part of the Netherlands Organization for Scientific Research (NWO) under grant number 056-11-012. This quick-result project is embedded in the pillar “The Healthy Brain, Program Cognitive Rehabilitation”.

The studies described in this thesis were financially supported by the University of Groningen, Faculty of Behavioural and Social Sciences, Department of Clinical & Developmental Neuropsychology.




**ISBN digital version**
978-94-034-1494-2

**ISBN printed version**
978-94-034-1495-9

**Cover design**
Anne Femke Vlagsma
*cover image inspired by the ‘Parkinson-tulip’*

**Design/lay-out**
Tjibbe Hoogstins

**Print**
Ipskamp Printing, Enschede

rijksuniversiteit groningen

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## Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 25 april 2019 om 14:30 uur

door

Thialda Teakje Vlagsma

geboren op 15 april 1987
te Sneek

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**Chapter 1**

# General introduction

# Parkinson's disease

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The first symptoms usually become manifest between 50 and 60 years of age (Wolters, van Laar, & Berendse, 2007). In general, the incidence and prevalence rates rise with increasing age, with males being more affected than females (females ≥40 years 37.55 per 100.000 person-year, males ≥40 years 61.21 per 100.000 person-year) (Hirsch, Jette, Frolkis, Steeves, & Pringsheim, 2016; Pringsheim, Jette, Frolkis, & Steeves, 2014). The prevalence of Parkinson's disease worldwide is 315 per 100.000 persons (Pringsheim et al., 2014).

The clinical presentation of PD is predominantly characterised by motor symptoms, such as bradykinesia (slowness and diminished amplitude of movement), akinesia (loss of movement), resting tremor, rigidity and postural instability (Jankovic, 2008). However, also a variety of non-motor symptoms such as cognitive impairments, neuropsychiatric symptoms (e.g. depression, hallucinations), autonomic dysfunctions (e.g. orthostatic hypotension), sleep disorders and fatigue can occur in PD (Lohle, Storch, & Reichmann, 2009). Non-motor symptoms may disproportionately magnify disability, increase the need for supervision, and affect emotional aspects of the relationship with a caregiver (Mosley, Moodie, & Dissanayaka, 2017). The PD symptoms are especially caused by a progressive degeneration of dopamine producing neurons in the substantia nigra and the ventral tegmentum, which belong to the basal ganglia (Wolters et al., 2007; Zgaljardic et al., 2006). Also, alterations in the noradrenergic, serotonergic and cholinergic transmitter systems play a role in the etiology of the disease.

The substantia nigra and ventral tegmentum are key elements of the frontostriatal circuits. The dopamine driven frontostriatal circuits in PD can be divided in a "sensorimotor circuit", an "associative, cognitive circuit" and a "limbic circuit" (see figure 1). In each of these circuits, specific parts of the frontal cortex (motor and premotor frontal areas, dorsolateral prefrontal cortex and orbitofrontal cortex) are connected to specific parts of the striatum and subsequently to functionally segregated parts of other structures within the basal ganglia (e.g. pallidum, subthalamic nucleus and thalamus) in a topographical manner. The sensorimotor circuit is important for motor behaviour, the associative, cognitive circuit is involved in cognitive and executive functions (such as initiative and drive) and the limbic circuit is related to regulation of emotional and decision-making aspects of behaviour (Zgaljardic et al., 2006). Thus, if the dopaminergic input is decreased over time in patients with PD, this will have an impact not only on motor function, but also on cognition and behaviour. However, Bohnen and colleagues (2018a; 2018b)

demonstrated that cognitive decline is more severe when there is also disintegration of the cholinergic system.

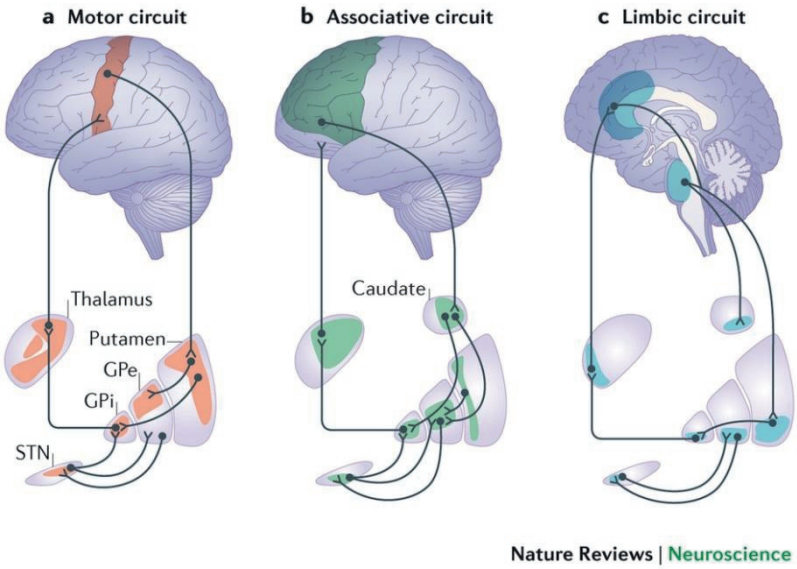


**Figure 1**. Functional organisation of the basal ganglia. The basal ganglia are divided into motor (A), associative (B), and limbic (C) subregions, which are topographically segregated, as highlighted by areas coloured in red (motor cortex), green (prefrontal cortex), and blue (anterior cingulate cortex). Figure reprinted from Obeso and colleagues. GPe=globus pallidus pars externa. GPi=globus pallidus pars interna. STN=subthalamic nucleus. (Rodriguez-Oroz et al., 2009).

## Cognitive impairments in Parkinson's disease

In patients with PD about 25% show mild cognitive impairment (MCI) at onset, with increasing frequency rates (39.4%) as disease severity progresses (Kalbe et al., 2016). The presence of MCI is of clinical relevance, since it has been found to predict the risk of developing PD dementia (Domellof, Ekman, Forsgren, & Elgh, 2015). According to the Movement Disorders Task Force criteria, MCI is defined as 1) a gradual decline in cognitive ability reported by either the patient or informant or observed by the clinician, 2) cognitive impairments on neuropsychological testing or a screening of global cognitive abilities and 3) cognitive impairments that are not sufficient to interfere significantly with daily life functioning (Litvan et al., 2012). MCI can be subdivided into single versus multiple domain MCI and amnestic versus non-amnestic MCI, based on the specific profile of cognitive impairments within the domains of memory, executive functions (EF), attention, visuospatial functions and language. In the study of Kalbe et al. (2016), MCI single domain was operationalised as one impaired test result (i.e. at least 1.5 SD < normative mean) within one cognitive

domain and MCI multiple domain as at least one affected test result in at least two domains. If impairments were found related to memory tests, MCI was defined as amnestic. Findings showed that 39.4% of the MCI subtypes were non-amnestic single domain, 30.5% amnestic multiple domain, 23.4% non-amnestic multiple domain and 6.7% amnestic single domain. Thus, findings indicate that the MCI non-amnestic subtype is more frequently found than the amnestic subtypes. EF appeared to be the most affected cognitive domain (Kalbe et al., 2016), which is in line with previous findings (Moustafa & Poletti, 2013; Muslimovic, Post, Speelman, & Schmand, 2005).

# Executive functions

Given that the dopaminergic frontostriatal networks become dysfunctional in PD, it is not surprising that impairments in executive functions (EF), which are predominantly regulated by prefrontal areas, are frequently observed in PD (Jurado & Rosselli, 2007; Zgaljardic et al., 2006). These impairments are frequently present in the early stages of the disease and are even observed in newly diagnosed patients (Dirnberger & Jahanshahi, 2013; Elgh et al., 2009; McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Muslimovic et al., 2005).

EF enable us to behave in a goaldirected way, to set and achieve realistic life goals and to adapt our behaviour to changing conditions (Burgess & Simons, 2005; Lezak, 1982). EF are mainly required in new, non-routine and complex situations. EF is an umbrella term encompassing several aspects, but to date still no consensus has been reached on which specific functions are defined as EF (Jurado & Rosselli, 2007). There is no uniformity of the concept EF, as shown in a review which detected 68 different definitions of subcomponents of EF in 60 different studies (Packwood et al. (2011).

However, we will use in this thesis a more condensed definition of EF, which distinguishes eight essential and clinical relevant aspects of EF: *self-awareness* of strengths and needs, realistic and concrete *goal-setting, planning* the steps to these goals, *self-initiating* these plans, *self-monitoring* and evaluating performance according to plan and goal, *self-inhibiting* behaviour not leading to the goals set, *flexibility and problem solving* when situations cannot be dealt with according to plan and *strategic behaviour* (Ylvisaker, (1998).

# Neuropsychological assessment of executive functions

Measurement of EF is quite challenging, using either objective and/or subjective methods. Neuropsychological tests are commonly used to measure impairments in EF in an objective way, as opposed to questionnaires, that can be considered as more subjective. A neuropsychological test setting is a standardised environment which

offers structure by administering neuropsychological tests in a fixed order and providing patients with detailed instructions (including cues to initiate behaviour). Also, external distractions are minimised in order to optimize patients' focused attention on task execution. In case of measuring EF this is disadvantageous, since EF are especially required in non-routine, complex and unstructured situations, in which one needs to make a plan of action and self-initiate this plan. Standard neuropsychological tests, such as the Trail Making Test and Stroop Color-Word test might therefore not tap the aspects of EF in the same way as they are tapped in everyday life situations. This implies that the ecological validity of standard neuropsychological tests might be rather low (Burgess et al., 2006; Manchester, Priestley, & Jackson, 2004). The Behavioural Assessment of the Dysexecutive Syndrome (Wilson, Alderman, Burgess, Emslie, & Evans, 1996b) has been specifically designed as a test battery for EF with a higher ecological validity. Its predictive value for functioning in everyday life is still limited, although higher than using standard tests (Norris & Tate, 2000; Wood & Liossi, 2006).

Questionnaires (e.g. Dysexecutive Syndrome (DEX)) measure the extent to which patients and/or their significant others actually experience executive impairments in everyday life and to what extent they experience this as burdensome. Although these measures are subjective, they might give a better view of EF problems in everyday life than is provided by neuropsychological tests. However, a general problem of this subjective method is, that in case patients have impaired self-awareness (which is part of EF dysfunctions and common among neurological patient groups) they tend to underestimate their executive problems and as such are not able to give an accurate representation of their actual functioning. Proxy-reports of patients' significant others are in this case essential. In a previous study no evidence was found that impaired self-awareness played a role in the assessment of EF in patients with PD, since no significant difference was found between patient and proxy reports of the DEX (Koerts et al., 2012).

## Impact of EF on everyday life functioning and QoL of patients with PD

Previous studies have shown that in patients with PD several executive dysfunctions can occur. Deficits in internal control of attention, set shifting (i.e. flexibility), planning, inhibition, conflict resolution (i.e. problem solving), impairments in dual task performance (i.e. multitasking) and impairments on a range of decision-making and social cognition tasks are being most frequently reported (Dirnberger et al., 2013). These EF are essential for performing goal-directed behaviour in daily life. Therefore it is not surprising that patients with PD and executive dysfunctions become increasingly

impaired in planning, organizing and executing daily life activities (Bronnick, 2006). Patients need to plan and execute daily task more sequentially and controlled, because the required capacities for parallel and automatic processes of multitasking become impaired (Koerts et al., 2011). For example, walking while performing another task (e.g. phone someone), managing medication intake at fixed time intervals in relation to eating and drinking or driving (Bronnick et al., 2006; Manning et al., 2012; Wu, Hallett, & Chan, 2015) can become very challenging activities. Patients with PD also reported themselves that impairments in EF contribute significantly to a decreased independence in everyday life activities (E. Foster & Hershey, 2011) and subsequently to a lower Quality of Life (QoL) (Kudlicka, Clare, & Hindle, 2014; Lawson et al., 2014a).

# Neuropsychological rehabilitation

According to the World Health Organization's International Classification of Functioning, Disability and Health (ICF), a disease can affect patients' functioning on different levels: on the functional level (i.e. cognitive or physical impairments), on the activity level and on the patients' level of participation in societal domains (i.e. work, social relations, leisure and mobility) (Heerkens, Hirs, de Kleijn-de Vrankrijker, van Ravenberg, & ten Napel, 2002). Neuropsychological rehabilitation aims to help patients and their relatives to cope with the cognitive, emotional, social and behavioural consequences of (acquired) brain injury and, if possible, to improve these problems. As shown in figure 2, cognitive rehabilitation is part of the broader field of neuropsychological rehabilitation and is specifically aimed at the cognitive consequences of brain injury and disease. Cognitive rehabilitation consists of psycho-education, making practical adjustments to patients' living environment and cognitive training. Cognitive training can aim at improvement at different levels of functioning, which are consistent with the levels of functioning as distinguished by the WHO. Cognitive training on the functional level (defined as "cognitive training" in chapter 6) aims at recovery of underlying cognitive functions by repetitive practise of (computerised) tasks that require the use of specific cognitive functions that are impaired. Skills training focuses on repetitive training of specific activities in everyday life in which patients encounter cognitive impairments. Strategy training involves learning cognitive strategies by making use of intact cognitive functions in order to help patients compensate for their cognitive impairments in everyday life. Compared to function and skills training, strategy training aims to improve patients' level of participation more in general and exceeds the level of improving only specific activities in everyday life.

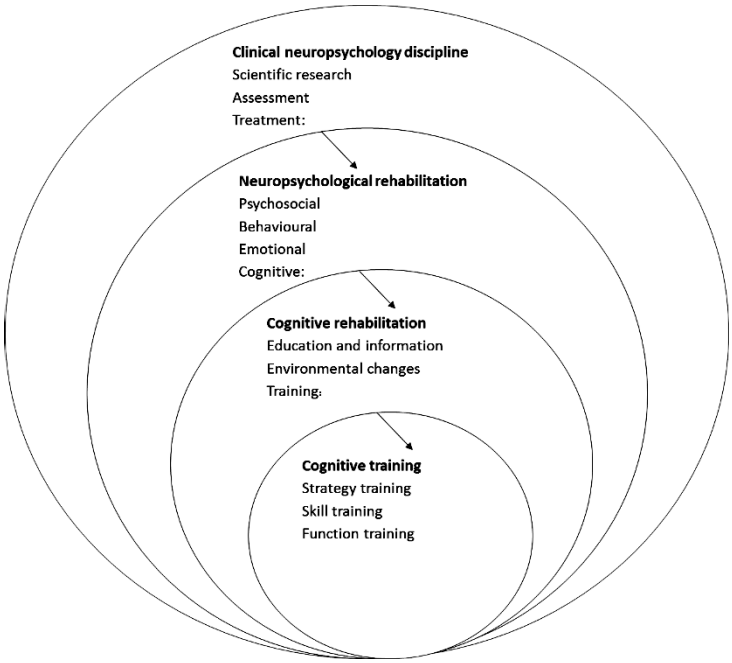


**Figure 2.** Framework of neuropsychological interventions that are used in clinical neuropsychology (Kessels, Eling, Ponds, Spikman, & van Zandvoort, 2017).

In recent literature reviews, cognitive rehabilitation and in particular strategy training has been proven beneficial and is recommended as treatment option for executive impairments in patients with different types of acquired brain injury (e.g. traumatic brain injury and stroke) (Cicerone et al., 2011; Krasny-Pacini, Chevignard, & Evans, 2013). These treatment programmes include generally session of 1 to 2 hours in length over a 3-6 month period, depending on the session frequency (usually once or twice a week) (Tate et al., 2014). In patients with neurodegenerative disorders such as PD, cognitive rehabilitation is not yet part of the standard therapy.

Based on the aforementioned topics, the aim of this thesis was to answer two main questions. The first question was how impairments in EF in patients with Parkinson's disease could be characterised related to their assessment and how these impairments interfere with everyday life. It was hypothesised that impairments in EF are mainly apathy driven and can be explained partly by underlying slowness of motor and cognitive processes. The other main question to answer was if cognitive treatment would improve impairments in EF of patients with PD in everyday life? Our hypothesis was that strategy training would be more effective as compared to computerised training of specific cognitive functions.

# Thesis outline

According to the main research questions, this thesis is divided into two sections. The first part, chapter two and three, focuses on the neuropsychological assessment of EF, slowness and their interrelationship in patients with PD. The other part (chapter four, five and six) centres around the topic of cognitive rehabilitation for impairments in EF in patients with PD. Most importantly, the effectiveness of ReSET; a Strategic Executive Treatment was evaluated in a group of patients with PD.

In **chapter two** it was examined whether patients with PD show mental slowness apart from motor slowness. If this was the case, the secondary aim was to determine to what extent mental slowness affects patients' performance on neuropsychological tests of attention, memory and EF.

The first aim of the study in **chapter three**, was to examine whether impairments in EF as objectified with tests are associated with complaints about impairments in EF in everyday life, as reported on subjective questionnaires. The second aim was to determine to what extent level of participation and QoL of patients with PD can be predicted by impairments in EF as measured with objective neuropsychological test measures versus subjective questionnaires.

The main question studied in **chapter four** is: are there reasonable arguments to assume that patients with PD cannot benefit from cognitive treatment programmes aimed to improve EF? PD patients' profile of executive impairments on neuropsychological tests and a questionnaire (Dysexecutive Syndrome: DEX), and treatment goals related to executive impairments in everyday life were compared to the executive profile and goals of patients with ABI, for whom cognitive treatment for executive impairments is commonly accepted.

**Chapter five** comprises a review of studies that have been conducted on cognitive rehabilitation in patients with PD so far (up to 2013). Herewith, we were specifically interested in the extent to which the studied cognitive treatment programmes focused on improving EF, in whether strategy training was applied and in methodological aspects (i.e. methodological quality and type of outcome measures that were used).

**Chapter six** presents the results of our randomised controlled trial in which we investigated according to our hypothesis whether ReSET, a Strategic Executive Treatment, is more effective than a computerised function training for aspects of attention (Cogniplus) in improving executive impairments in daily life and level of participation in PD.

A general discussion of the preceding chapters is presented in **chapter seven**. The focus is on interpreting the main outcomes of the RCT in terms of their clinical relevance. Recommendations for future research are discussed as well.

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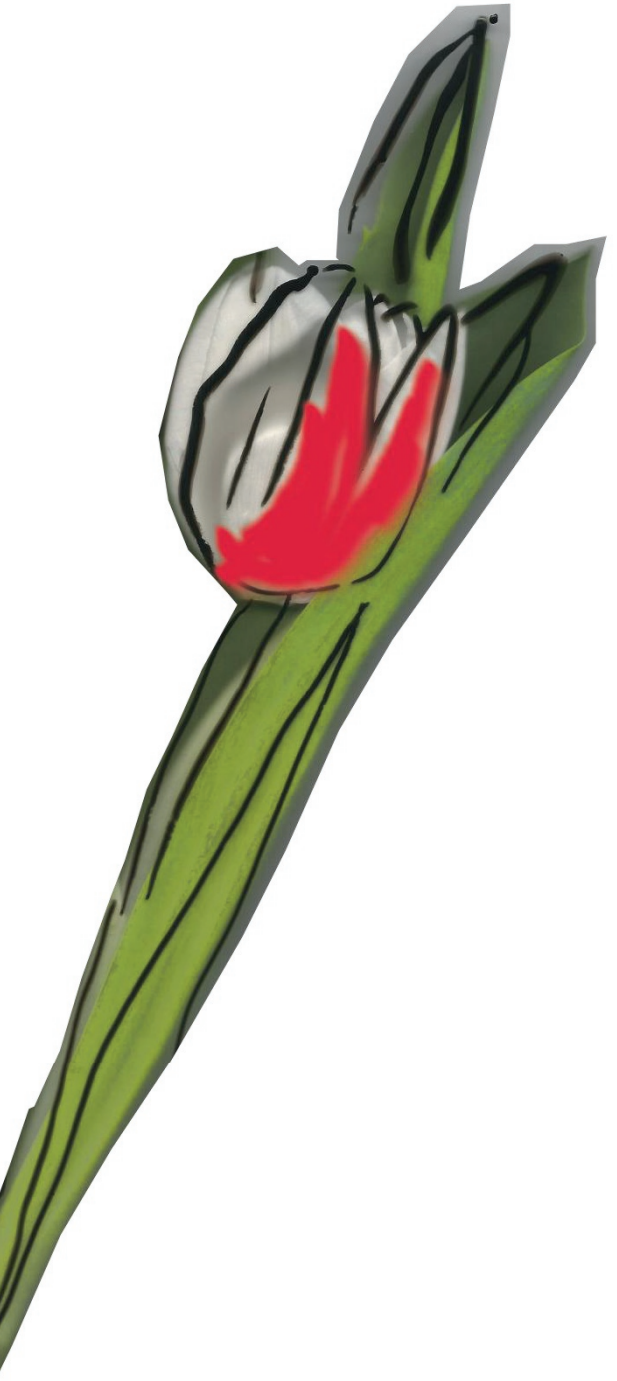

## Chapter 2

# Mental slowness in patients with Parkinson's disease: associations with cognitive functions?

**Published as:** Vlagsma, T. T., Koerts, J., Tucha, O., Dijkstra, H. T., Duits, A. A., van Laar, T., & Spikman, J. M. (2016). Mental slowness in patients with parkinson's disease: Associations with cognitive functions? *Journal of Clinical and Experimental Neuropsychology, 38*(8), 844-852. doi:10.1080/13803395.2016.1167840 [doi]

# Abstract

**Introduction**
Motor slowness (bradykinesia) is a core feature of Parkinson's disease (PD). It is often assumed that patients show mental slowness (bradyphrenia) as well, however evidence for this is debated. The aims of this study were to determine whether patients with PD show mental slowness apart from motor slowness and, if this is the case, to what extent this affects their performance on neuropsychological tests of attention, memory, and executive functions (EF).

**Methods**
Fifty-five nondemented patients with PD and 65 healthy controls were assessed with a simple information-processing task in which reaction and motor times could be separated. In addition, all patients and a second control group (*N*=138) were assessed with neuropsychological tests of attention, memory, and EF.

**Results**
While patients with PD showed significantly longer reaction times than healthy controls, their motor times were not significantly longer. Reaction and motor times were only moderately correlated and were not related to clinical measures of disease severity. Patients with PD performed significantly worse on tests of attention and EF, and for the majority of neuropsychological tests 11-51% of the patients showed a clinically impaired performance. Reaction times did not, however, predict patients' test performance, while motor times were found to have a significant negative influence on tests of attention.

**Conclusions**
Patients with PD show mental slowness, which can be separated from motor slowness. Neuropsychological test performance is not influenced by mental slowness however, motor slowness can have a negative impact. When interpreting neuropsychological test performance of patients with PD in clinical practice, motor slowness needs to be taken into account.

# Introduction

The diagnosis of Parkinson's disease (PD) is based on the presence of motor symptoms, with bradykinesia being the single most important diagnostic sign (Wolters et al., 2007). Bradykinesia manifests itself as visible slowness and diminished amplitude of movement (Hughes, Daniel, Kilford, & Lees, 1992). Slowness is, however, assumed to be associated not only with motor behaviour in PD, but with mental information processing as well. This mental equivalent of bradykinesia is called bradyphrenia or mental slowness (Revonsuo, Portin, Koivikko, Rinne, & Rinne, 1993; Wolters et al., 2007).



The presence of mental slowness in patients with PD is, however, a subject of discussion. Several studies found evidence for the presence of mental slowness (Berry, Nicolson, Foster, Behrmann, & Sagar, 1999; Gauntlett-Gilbert & Brown, 1998; Hsieh, Chen, Wang, & Lai, 2008; Muslimovic et al., 2005; Revonsuo et al., 1993; Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002), whereas other studies could not demonstrate mental slowness in PD (Duncombe, Bradshaw, Iansek, & Phillips, 1994; Helscher & Pinter, 1993; Phillips et al., 1999). A possible explanation for this lack of consensus is that a broad variety of measures is used to assess speed of information processing as an indication of mental slowness. Some measures also include the measurement of higher order cognitive functions such as memory or executive functions (EF) (Albinet, Boucard, Bouquet, & Audiffren, 2012). Furthermore, previously many studies aimed to assess speed of information processing as an indication of mental slowness, but used measures that also included a manual motor response. However, in terms of neural networks, a global distinction can be made between the central processes of planning, preparing, and initiating a motor response and the physical execution of that manual motor response (i.e. peripheral nervous system). The central processes primarily involve activity in the prefrontal cortex, the supplementary, premotor cortex and the primary motor cortex, whereas the actual motor response involves primarily muscle activity in the arm and hand (Wolters et al., 2007). Since peripheral motor dysfunction is common in certain patient populations (e.g. patients with dystonia, Huntington's disease, and PD), it is crucial to distinguish between the assessment of speed of mental information processing and motor speed (Salthouse, 1994; Salthouse, 1996) when determining actual mental slowness. For this purpose, information-processing tasks that allow differentiation between reaction time (i.e. measure of information processing speed as an indication of mental slowness) and motor time are preferred to more standard neuropsychological tests that include manual or verbal motor activity (e.g. Trail Making Test or Stroop), which do not allow disentanglement of both components. To our knowledge, such tasks have not yet been applied to study the concepts of mental and motor slowness in

patients with PD. Therefore, our main objective was to examine whether mental and motor slowness could be measured separately and consequently whether these can be differentiated from each other in patients with PD using such a paradigm. Based on the assumption that bradykinesia and bradyphrenia are characteristic clinical signs of PD, we expect this to be demonstrated by longer motor as well as longer reaction times of patients with PD than of healthy controls. On the other hand, since we assume bradykinesia and bradyphrenia to be distinguishable concepts, it is hypothesised that motor and reaction times can be correlated, but do not show a one-to-one relationship.

Furthermore, if patients with PD exhibit mental slowness, the second aim is to determine to what extent this mental slowness influences the performance on neuropsychological tests. Neuropsychological tests are frequently used for the assessment of cognition in patients with PD and have demonstrated that cognitive impairments, especially within the domains of attention, memory, and EF, are common in this group (Elgh et al., 2009; Muslimovic et al., 2005). However, the majority of tests contain either a direct (outcome is measured as time of completion, e.g.: Trail Making Test) or an indirect (presentation of stimuli at a fixed pace, e.g.: Rey Auditory Verbal Learning Test) speed component. It seems therefore likely that impaired performances of patients with PD on such tests can, at least partially, be explained by their mental slowness. So far, only a small number of studies investigated the influence of mental slowness on cognitive test performance. Both Albinet et al. (2012) and Salthouse (1992) showed that mental slowness (partially) accounted for healthy participants' age-related differences in cognitive test performance. Moreover, differences on tests for focused and divided attention between patients with traumatic brain injury and healthy controls disappeared when scores were controlled for mental slowness (Spikman, van Zomeren, & Deelman, 1996). Only one study investigated the role of mental slowness in patients with PD and concluded that mental slowness was not related to executive functioning (Liozidou, Potagas, Papageorgiou, & Zalonis, 2012). Knowledge about the influence of slowness on neuropsychological tests performance is crucial in clinical practice, since it has to be determined whether impaired test performance can be interpreted as deficits of memory, attention and EF, or has to be attributed to slowness of information processing. Since most neuropsychological tests require also manual or verbal motor activity, the effect of motor slowness on neuropsychological test performance is examined as a subquestion. Finally, it is determined to what extent motor slowness, as measured with an information-processing task, and motor symptoms and disease severity, as measured with more clinical measures (Unified Parkinson's Disease Rating Scale motor section UPDRS-III, and the Hoehn and Yahr scale H&Y) are associated.

# Methods

## Participants

Fifty-five patients with idiopathic PD who were diagnosed according to the UK Parkinson's Disease Brain Bank Criteria were included. Exclusion criteria were dementia (i.e. SCales for Outcomes in PArkinson's disease-COGnition, SCOPA-COG, score ≤17;) (Verbaan et al., 2011) and other severe neurological and psychiatric comorbid conditions. Patients were recruited at the Department of Neurology of three medical centres in The Netherlands. Neuropsychological assessment was conducted while patients were on their regular dopaminergic medication and in the on phase. Four patients were not on dopaminergic therapy, and two patients did not report their current medication use. Furthermore, five patients underwent Deep Brain Stimulation (targets: subthalamic nucleus *N*=3, globus pallidus *N*=1, thalamus *N*=1), which was performed more than one year prior to study inclusion. A Levodopa equivalent daily dose(LEDD) was calculated for all patients who were on dopaminergic medication (Esselink et al., 2004). The UPDRS-III and the H&Y scale were used to assess disease severity. Patients in H&Y stages 4 and 5 were not included in this study. The study was approved by the medical ethical committee and was conducted in accordance with the declaration of Helsinki. All patients gave written informed consent.

In addition, data of two healthy control groups were used that came from several sources. Exclusion criteria were major neurological diseases and/or psychiatric disorders. One control group (HC1: *N*=65) was assessed with the simple information-processing task (see below for a detailed description of this task); data were provided by Schuhfried GmbH test company, Vienna, Austria. PD patients' performances on neuropsychological tests were compared to data of a second group of healthy controls (HC2), who were assessed with all neuropsychological tests that were used in the present study, except for the simple information-processing task. HC2 was composed out of healthy controls that were included in our previous studies. For tests of attention, memory and EF the number of controls with available data ranged from *N*= 77 (Stroop) to *N*= 136 (Zoo map). For the Rey Auditory Verbal Learning Test (RAVLT), data of 32 controls were available. Table 1 shows descriptive variables and disease characteristics of patients with PD and both healthy control groups. Level of education of all participants was classified on a 5-point scale ranging from (1) uncompleted or special education: < 9 years of education, to (5) completed university (of applied sciences).

**Table 1. Descriptive and disease characteristics of PD patients and healthy control groups.**

| | PD | | HC1 | | HC2 | |
|---|---|---|---|---|---|---|
| | M (SD) | Range | M (SD) | Range | M (SD) | Range |
| Age in years | 61.0 (9.5) | 42 - 79 | 63.1 (5.1) | 55 - 80 | 59.0 (7.6) | 38 - 87 |
| Education | 4.0 (1.0) | 2 - 5 | 3.0 (1.0) | 2 - 5 | 3.0 (1.0) | 2 - 5 |
| Sex | | | | | | |
| Male n (%) | 36 (65.5) | | 41 (63.1) | | 72 (52.2) | |
| Female n (%) | 19 (34.5) | | 24 (36.9) | | 66 (47.8) | |
| UPDRS-III | 21.2 (8.2) | 8 - 46 | | | | |
| H&Y | 2.5 (0.5) | 1 - 3 | | | | |
| LEDD | 731.3 (457.8) | 0 - 2080.0 | | | | |
| SCOPA-COG | 28.8 (4.4) | 19 - 37 | | | | |

*Note.* Educational level was classified on a 5-point scale; 1= unfinished or special education, < 9 years of education, 5= Bachelor or Master's degree. PD = Parkinson's disease; HC = healthy controls; UPDRS-III = Unified Parkinson's Disease Rating Scale Part III, motor section, range = 0-108 maximum; H&Y = Hoehn and Yahr scale, range = 0-5 maximum; LEDD = levodopa equivalent daily dose. SCOPA-COG= SCales for Outcomes in PArkinson's Disease – COGnition, range = 0-43 maximum.

## Neuropsychological assessment

### *Speed of information processing*

The simple information-processing task (S1 condition) of the Vienna Test System (Prieler, 2008) was used to measure reaction time and motor time separately. During the task, the participants' dominant index finger rested on a key (rest key). A black circle was constantly present in the middle of the lower half of the screen and as soon as this circle turned yellow, participants were instructed to lift their index finger and to press the response key as fast as possible. The distance between the rest key and the response key was 5.5 cm. The interstimulus interval ranged between 1.5 to 6.5 s, and the duration of the presentation of the yellow circle was 1 second. The task consisted of five practise trials and 28 test trials. For each participant, two scores were calculated: (a) mean reaction time (RT), that is, the mean time between the appearance of the target stimulus and lifting the dominant index finger over all correctly completed trials and (b) mean motor time (MT), i.e. the mean time between lifting the dominant index finger and pressing the response key over all correctly completed trials. Both reaction time and motor time were measured in milliseconds.

### *Neuropsychological tests of attention, memory, and executive functions*

The Trail Making Test part A (TMT; in seconds) (Reitan, 1958) and the Stroop Word Card (in seconds) (Stroop, 1935) were used to assess attention. Short-term verbal memory was measured with the Digit Span Forward (total score) (Wechsler, 1987). The Rey Auditory Verbal Learning Test (Dutch version; RAVLT) (Deelman, Brouwer, van Zomeren, & Saan, 1980) is a verbal memory test that was used to measure immediate recall (IR; max. score=75) and delayed recall (DR; max. score=15) of unrelated verbal information. EF were assessed with the TMT B/A ratio (Reitan, 1958) and Visual elevator (Test of Everyday Attention; TEA, max. score=10) (Robertson, Ward, & Ridgeway, V. & Nimmo-Smith, I., 1994), Stroop Color-Word/Color card ratio (Stroop, 1935), and the subtest Zoo map (total score) of the Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Wilson et al., 1996b).



## Statistical analyses

IBM Statistical Package for the Social Sciences version 22 was used for data analysis. Analyses of covariance (ANCOVAs) with age, gender, and level of education included as covariates were used to compare the performances of patients with PD and healthy controls on the simple information-processing task and neuropsychological tests (Table 2 and 3). For statistical analysis an alpha of .05 was applied. In case of multiple comparisons (Table 3) a Bonferroni-corrected alpha was used per cognitive domain. Furthermore, effect sizes for group differences were calculated (Cohen's *d)*. Correlations were calculated to determine the associations between the RT, MT, UPDRS, neuropsychological tests (Pearson's *r*), and H&Y (Spearman's $r_s$*)*. Performances of patients with PD and controls on the simple information-processing task and other neuropsychological tests were also analysed from a clinical perspective, that is, performances on tests were compared to representative normative data as provided by the test developers. Performances that fell within the lowest 10% of the normative samples were considered as being impaired (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Finally, hierarchical linear regression analyses (method: enter) were used to study the influence of speed of information processing on patients' performances on each neuropsychological test separately. The assumptions for regression analyses were met. MT (block 1) and RT (block 2) were respectively included as independent variables into each model. Scores on tests of attention (TMT A and Stroop Word Card), memory (Digit Span Forward and RAVLT), and EF (TMT B/A, Stroop ratio, Visual elevator and Zoo map) were dependent variables.

# Results

## Demographic data

No differences were found between HC1 and patients with PD with regard to age (t = -1.46, $p$ = .149), gender ($\chi^2$ = 0.07, $p$ = .787) and level of education (Mann-Whitney U = 1617.50, $p$ = .342). Overall, there were also no differences between patients with PD and HC2 in age (t = 1.39, $p$ = .167), gender ($\chi^2$ = 2.81, $p$ = .093), and level of education (Mann-Whitney U = 3232.00, $p$ = .086). The RAVLT subgroup of HC2 ($N$=32) did not differ from patients with PD with regard to age (t = -0.15, $p$ = .878) and gender ($\chi^2$ = 2.01, $p$ = .156). However, level of education was significantly different between this subgroup and patients with PD (Mann-Whitney U = 585.50, $p$ = .006). Because the results show some trend-level differences between patients and controls and since it is known that age, gender and level of education can be of influence on cognitive test performance, these demographic variables were included as covariates in further analyses. Demographic data are presented in Table 1.

## Simple information-processing task and neuropsychological test performance

In comparison to healthy controls, patients with PD showed a significantly slower RT (medium effect size, see Table 2). No differences were found between groups with regard to MT. From a clinical perspective, the simple information-processing task revealed clinically impaired mental slowness in 11% of patients with PD and clinically impaired motor slowness in 7% of patients with PD (performance ≤ lowest 10% of normative sample). In the healthy control group, 5% of controls showed clinically impaired mental slowness and 6% impaired motor slowness. The percentage of impairments did not significantly differ between groups for both mental and motor slowness (RT: $\chi^2$ = 1.70, $p$ = 0.192; MT: $\chi^2$ = 0.38, $p$ = .536).

**Table 2. Performances of PD patients and healthy controls on the simple information-processing task of the Vienna Test System.**

| | PD | HC1 | ANCOVA | Covariates | | | ES |
|---|---|---|---|---|---|---|---|
| | M (SD) | M (SD) | F (p) | Age | Sex | Edu | *d* |
| Simple information-processing task | | | | | | | |
| Motor time | 232.73 (78.64) | 218.35 (72.19) | 1.97 (0.163) | ns | ns | ns | 0.19 |
| Reaction time | 363.53 (84.67) | 316.34 (75.93) | 10.10 (0.002)* | ns | ns | ns | 0.60 |

*Note.* PD = Parkinson's disease; HC = healthy controls; ANCOVA = analysis of covariance; ES = effect size; Edu = education. Times in ms. *$p$<0.01; covariates.

A significant but moderate correlation was found between the RT and MT of the simple information-processing task (patients with PD: $r$ = .40, $p$ = .003; controls: $r$ = 0.41, $p$ = .001). In addition, no significant associations were found between the scores on the UPDRS-III and H&Y and the RT and MT (RT and H&Y: $r_s$ = .11, $p$ = .465, RT and UPDRS: $r$ = .17, $p$ = .227, MT and H&Y: $r_s$ = .09, $p$ = .553, MT and UPDRS: $r$ = .23, $p$ = .108).

Table 3 presents the average performance of patients with PD and healthy controls on tests of attention, memory and EF. Patients with PD performed significantly worse than healthy controls on tests of attention and on the Zoo map. Groups did not differ with regard to the performances on other tests of EF and memory. However, for six out of nine tests, 11 to 51% of PD patients' test scores were considered as clinically impaired.



**Table 3. Performances of patients with PD and healthy controls on tests of cognition.**

| | PD | | HC2 | ANCOVA | | Covariates | | | ES |
|---|---|---|---|---|---|---|---|---|---|
| | %≤ 10th pc (N) | M (SD) | M (SD) | F | *p* | Age | Sex | Edu | *d* |
| Attention | | | | | | | | | |
| TMT A | 25.5 (14) | 43.18 (13.19) | 33.34 (9.40) | 24.38 | <0.001* | * | ns | ns | 0.90 |
| Stroop Word Card | 50.9 (28) | 50.96 (9.66) | 47.16 (7.68) | 5.02 | 0.027* | * | ns | ns | 0.44 |
| Memory | | | | | | | | | |
| Digit span forward | 3.6 (2) | 8.73 (1.65) | 8.82 (1.69) | 0.06 | 0.815 | * | ns | ns | 0.05 |
| RAVLT IR | 35.2 (19) | 38.35 (11.25) | 38.84 (10.36) | 0.53 | 0.470 | * | * | * | 0.04 |
| RAVLT DR | 11.1 (6) | 7.85 (3.14) | 7.38 (3.38) | 0.40 | 0.528 | ns | * | * | 0.15 |
| EF | | | | | | | | | |
| TMT ratio | 20.0 (11) | 2.48 (0.93) | 2.17 (0.53) | 4.64 | 0.033 | * | ns | ns | 0.44 |
| Stroop ratio | 3.6 (2) | 1.64 (0.28) | 1.54 (0.18) | 4.73 | 0.032 | * | ns | * | 0.41 |
| Visual elevator total score | 18.2 (10) | 7.83 (2.28) | 8.44 (1.65) | 2.42 | 0.122 | * | ns | ns | 0.32 |
| Zoo map total score | 27.3 (22) | 8.29 (5.68) | 10.84 (4.71) | 10.49 | 0.001* | * | ns | * | 0.51 |

*Note.* *Significant p-value< Bonferroni corrected alpha. ŧANCOVA was conducted for the RAVLT IR and DR with level of education included as a covariate. ES = Effect Size. TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test: IR = immediate recall; DR = delayed recall; TMT ratio = TMT B/TMT A; Stroop ratio = Color-Word/Color card.

In Table 4 the univariate associations between MT, RT, and neuropsychological test performance of patients with PD are presented. A significant correlation was found between MT and the TMT A and Stroop ratio. RT also showed a significant correlation with the Stroop ratio. Consequently, hierarchical regression analyses were conducted to study whether neuropsychological test scores of patients with PD can be predicted from MT and RT. MT and RT were separately included (i.e. MT= block 1, RT= block 2) in the regression models to determine their individual contribution to the model.

**Table 4. Univariate Pearson's correlations between MT, RT and neuropsychological tests in patients with PD.**

| | MT | RT |
|---|---|---|
| Attention | | |
| TMT A | 0.31* | 0.16 |
| Stroop Word Card | 0.25 | 0.26 |
| Memory | | |
| Digit Span forward | -0.20 | -0.02 |
| RAVLT IR | -0.25 | -0.18 |
| RAVLT DR | -0.13 | -0.10 |
| EF | | |
| TMT ratio | 0.16 | 0.07 |
| Stroop ratio | 0.41* | 0.36** |
| Visual elevator total score | -0.10 | -0.21 |
| Zoo map total score | -0.17 | -0.05 |

*Note.* PD = Parkinson's disease; TMT = Trail Making Test; RAVLT = Rey Auditory Verbal Learning Test IR = immediate recall; DR = delayed recall; TMT ratio = TMT B/TMT A; Stroop ratio = Color-Word/Color card; MT = motor time; RT = reaction time; EF = executive functions. * $p < 0.05$, ** $p < 0.01$.

Table 5 shows that MT alone appeared to be a significant predictor of performance on the TMT A ($R^2 = 0.09$, $F(1, 54) = 5.53$, $p = .022$). However, when RT was included the model was no longer significant ($R^2 = 0.10$, $F(2, 54) = 2.77$, $p = .072$). Furthermore, a different pattern was found for the complete model of the Stroop Color-Word/Color card ratio. The complete model (including MT and RT) explained a significant percentage of variance in the Stroop Color-Word/Color card ratio ($R^2 = 0.22$, $F(2, 54) = 7.10$, $p = .002$), however only MT was found to contribute significantly to the model (see Table 5). For the other neuropsychological tests, neither the combination of MT and RT nor MT or RT separately were significant predictors of PD patients'

performances. The results of complete models were as follows: attention [Stroop Word Card: $R^2$ = 0.09, F(2, 54) = 2.67 , *p* = .079], memory [Digit Span Forward: $R^2$ = 0.05, F(2, 54) = 1.24 , *p* = .298, RAVLT IR: $R^2$ = 0.07, F(2, 54) = 2.00, *p* = .146 and RAVLT DR: $R^2$ = 0.02, F(2, 54) = 0.52, *p* = .597], and EF [TMT B/A ratio: $R^2$ = 0.02, F(2, 54) = 0.64, *p* = .532, Visual elevator: $R^2$ = 0.04, F(2, 51) = 1.12, *p* = .335 and Zoo map total score: $R^2$ = 0.03, F(2, 54) = 0.82, *p* = .444].

**Table 5. Predictors of PD patients' performance on tests of attention and EF based on hierarchical linear regression analysis.**

| | $R^2$ | $R^2$ change | B | β | t | *p* |
|---|---|---|---|---|---|---|
| Attention | | | | | | |
| TMT A | | | | | | |
| Constant | | | 31.187 | | 5.80 | <0.001** |
| Motor time | 0.09 | | 0.052 | 0.31 | 2.35 | 0.022* |
| EF | | | | | | |
| Stroop ratio | | | | | | |
| Constant | | | 1.093 | | 6.88 | <0.001** |
| Motor time | 0.17 | | 0.001 | 0.32 | 2.38 | 0.021* |
| Reaction time | 0.22 | 0.05 | 0.001 | 0.23 | 1.74 | 0.089 |

*Note.* PD = Parkinson's disease; EF = executive functions; TMT = Trail Making Test. Regression analysis, method: enter. *$p < 0.05$, **$p < 0.001$

# Discussion

To our knowledge, this is the first study that measures RT and MT separately in order to determine whether mental slowness can be differentiated from motor slowness in patients with Parkinson's disease. Patients with PD showed on average a significantly longer RT on a simple information-processing task than healthy controls. Surprisingly, PD patients' MTs were not significantly slower than healthy controls. This is remarkable since bradykinesia is a core feature of PD. These findings indicate that mental slowness can be present in patients with PD in the absence of motor slowness and strengthen findings of previous studies that demonstrated mental slowness in PD ,even though these studies did not use tasks that allowed the differentiation of mental and motor slowness (Berry et al., 1999; Gauntlett-Gilbert & Brown, 1998; Hsieh et al., 2008; Muslimovic et al., 2005; Revonsuo et al., 1993; Sawamoto et al., 2002).

The finding that mental and motor slowness are distinctive constructs was also substantiated by the moderate correlations between RT and MT in both patients and controls, which indicates that RT and MT only share a relatively small amount of

variance (i.e. 16%). Interestingly, clinical ratings of motor symptoms and disease severity (i.e. scores on UPDRS-III and H&Y scale) were related neither to RT nor to MT. A possible explanation for this finding is that standard clinical measures of motor symptoms in PD assess motor slowness (i.e. bradykinesia) in a different way from reaction time paradigms. The unexpected finding that patients did not show significantly slower MTs than healthy controls strengthens this interpretation. The UPDRS, for example, assesses motor slowness with several items that do not only ask the observer to evaluate the speed of a specific motor action, but also ask them to evaluate the amplitude, hesitations, and halts of the action per side of the body. Even though the bradykinesia subscale of the UPDRS is a valid measure of motor slowness (Buck, Wilson, Seeberger, Conner, & Castelli-Haley, 2011), to our knowledge the relation with reaction time paradigms has not been studied so far and may represent an interesting subject for future research.

The second aim of the current study was to determine the influence of mental slowness on neuropsychological test performance of patients with PD. This is relevant, because the majority of neuropsychological tests include a speed component (i.e. in the outcome measure or paced presentation of stimuli). Hence, PD patients' performances on these tests may be negatively influenced by disease-related mental slowness, which may have consequences for the interpretation of test results in clinical practice. The group of patients with PD that was included in the present study showed a profile of cognitive impairments that was consistent with previous studies (Koerts, Tucha, Lange, & Tucha, 2013; Muslimovic et al., 2005; Watson & Leverenz, 2010), indicating that a representative group of patients with PD was included. Results of regression analyses showed that RT as an indication of mental slowness did not predict PD patients' performances on any of the neuropsychological tests of attention, memory, and EF, which is in line with the findings of Liozidou et al. (2012). MT, on the other hand, was found to be a significant predictor of PD patients' performance on TMT A and the Stroop Color-Word/Color card ratio. With regard to the TMT A this is not surprising, since this paper-and-pencil test involves manual motor activity because it requires patients to search and connect succeeding numbers as fast as possible by drawing a line. Regarding the Stroop Color-Word/Color card ratio it seems that even though we used the ratio score that implies to control for the speed component (measured with the Color card), this measure still reflects motor behaviour that is, reading words out loud as fast as possible.

The current study has a few limitations that need to be mentioned. First, the heterogeneity of the patient group with regard to treatment (dopaminergic treatment *N*=44; nondopaminergic treatment/treatment unknown *N*=6; deep brain stimulation, DBS, *N*=5) is a limitation, since dopaminergic treatment and DBS can have positive as well as negative effects on cognition (Cools, Barker, Sahakian, & Robbins, 2001; Cools, Barker, Sahakian, & Robbins, 2003; Cools, 2006). When comparing, however, the

results on descriptive measures and the RT and MT between patients on dopaminergic treatment and patients who received DBS or of whom the treatment strategies were unknown, no differences were found (data not shown). Furthermore, when analysing the MTs, we did not control for possible minor on-off fluctuations. Since there were no significant differences between patients and controls regarding the MTs of the simple information-processing task, we assume that the minor on-off fluctuations did not negatively influence test performance. Another limitation is the use of the UPDRS-III total score instead of a sum score of the individual bradykinesia items. Since the total score also includes the evaluations of rigidity and tremor, it is possible that the association between the UPDRS-III and RT and MT would have been different when these items were excluded. Also, the use of normative data, without adjustments for age, gender and education, when determining the percentage of impaired RTs and MTs in patients with PD and healthy controls can be considered a limitation. However, when for example an age-related norm group was used, the size of the normative sample would have been substantially smaller. Therefore the use of a general norm group was preferred. Since the percentage of impaired performances on the simple information-processing task did not significantly differ between patients and controls, the sensitivity of the paradigm appears to be insufficient and must be considered a limitation. A final limitation is that for patients with PD the exact disease duration was not reported in this study. The possible influence of disease duration on test performance could therefore not be analysed.

In conclusion, patients with PD show mental slowness that can be separated from slowness of movement. However, this mental slowness did not have an influence on the performances of patients with PD on various neuropsychological tests for attention, memory and EF. Interestingly, patients showed no motor slowness on the simple information-processing task. Also, their MTs were not related to clinical measures of disease severity (including bradykinesia), indicating that both measures assess motor slowness in a different way. MTs did, however, determine patients' performance on two test measures of which the outcome was measured in terms of speed. We tentatively conclude that these findings indicate that mental slowness is not a substantial factor that needs to be taken into account when interpreting results of patients with PD on these neuropsychological tests. PD patients' motor speed, on the other hand, can be of influence on test performances and needs to be taken into consideration in clinical practice.

**Acknowledgements**
We are grateful to Schuhfried GmbH, in particular M. Vetter and R. Debelak, for the friendly cooperation and providing normative data for our analyses.

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## Chapter 3

# Objective versus subjective measures of Executive Functions: predictors of participation and Quality of Life in Parkinson Disease?

**Published as**: Vlagsma, T. T., Koerts, J., Tucha, O., Dijkstra, H. T., Duits, A. A., van Laar, T., & Spikman, J. M. (2017). Objective Versus Subjective Measures of Executive Functions: Predictors of Participation and Quality of Life in Parkinson Disease?. *Archives of physical medicine and rehabilitation*, *98*(11), 2181-2187.

# Abstract

**Objectives**
To determine whether objective (neuropsychological tests) and subjective measures (questionnaires) of executive functions (EF) are associated in patients with Parkinson's disease (PD), and to determine to what extent level of participation and quality of life (QoL) of patients with PD can be predicted by these measures of EF.

**Methods**
*Design:* Correlational research design (case-control and prediction design). *Setting*: Departments of neuropsychology of three medical centres in The Netherlands.
*Participants*: A sample (N=136) of patients with PD (N=42) and their relatives, and controls without PD (N=94).
*Main Outcome Measures*: A test battery measuring EF. In addition, patients, their relatives, and controls completed the Dysexecutive Questionnaire, Brock Adaptive Functioning Questionnaire, and Barkley Deficits in Executive Functioning Scale-time management questionnaires measuring complaints about EF. Participation and QoL were measured with the Impact on Participation and Autonomy scale and the Parkinson's Disease Questionnaire-39, respectively.

**Results**
Patients with PD showed impairments in EF on objective tests and reported significantly more complaints about EF than did controls without PD. No associations were found between patients' performances on objective and subjective measures of EF. However, both objective and subjective measures predicted patients' level of participation. In addition, subjective measures of EF predicted QoL in patients with PD.

**Conclusions**
These findings show that objective and subjective measures of EF are not interchangeable and that both approaches predict level of participation and QoL of patients with PD. However, within this context, sex needs to be taken into account.

# Introduction

Cognitive impairments, including impairments in executive functions (EF), are frequently found in patients with Parkinson's disease (PD) (Kudlicka, Clare, & Hindle, 2011; McKinlay et al., 2010). Impairments in EF can already be present in newly diagnosed patients with PD and have a negative influence on patients' level of participation (Klepac, Trkulja, Relja, & Babic, 2008; Vlagsma et al., 2015) and quality of life (QoL) (Kudlicka et al., 2014; Lawson et al., 2014b). EF is an umbrella term that encompasses several higher-order capacities important for adequate and independent daily living, because they enable us to adapt to new, nonroutine situations and to act in a goal-oriented way (Burgess & Simons, 2005).

Neuropsychological tests are used to measure impairments in EF objectively. However, these tests are usually administered in a standardised setting offering a large amount of structure; that is, detailed instructions are given and external distractions are minimised. Consequently, performances on objective basic neuropsychological tests (e.g. Trail Making Test, (Reitan, 1958)) might not reflect complex unstructured daily life situations that require higher-order aspects of executive functioning (Lezak, 1982), such as goal setting and planning. Therefore, the ecological validity of many standard tests of EF is considered to be low (Burgess et al., 2006; Manchester et al., 2004). The Behavioural Assessment of the Dysexecutive Syndrome (BADS, (Wilson, Alderman, Burgess, Emslie, & Evans, 1996a) is a neuropsychological test battery consisting of six subtests that is within the field of neuropsychology considered to be the most valid ecological measure for EF. The predictive value for the BADS for daily life functioning is higher than that for the regular EF tests, but still limited (Norris & Tate, 2000; Wood & Liossi, 2006). An example of a task that better resembles daily life executive functioning is the Executive Secretarial Task (EST) which is performance-based task as it was designed to be a simulation of a job assessment procedure (Lamberts, Evans, & Spikman, 2010). Also in the field of occupational therapy, performance-based assessments resembling daily life tasks (i.e. performance of daily life activities, such as cooking) are performed to measure EF in an ecologically valid way (Poulin, Korner-Bitensky, & Dawson, 2013). A large drawback of this kind of measures is that their assessment is more time-consuming than is the case for regular neuropsychological tests; for instance, the administration of the EST takes three hours. This makes this kind of performance-based measures less suitable for use in regular neuropsychological assessment.

In contrast to neuropsychological tests that allow objective measurement, questionnaires can be used to measure the subjective experience of EF problems as well as patients' and their relatives' burden related to these EF problems in daily life (Koster, Higginson, MacDougall, Wheelock, & Sigvardt, 2015). However, if patients

have impaired self-awareness, which is common in neurological disorders, self-report questionnaires might not give an accurate representation of patients' functioning. This problem can be partly overcome by using proxy versions, which may also give an indication of patients' self-awareness by comparing judgments of patients and their relatives. Furthermore, various other factors might influence self-reports of patients. For example, in patients with PD the presence of depression or anxiety has been found to have a negative influence on the number and severity of complaints (Koerts et al., 2012; Lehrner et al., 2014). The objective and subjective approaches thus measure problems in EF from a different perspective, and therefore it is important to study their mutual relation.

Previous studies showed that correlations between impairments in EF, measured with objective measures, and complaints about EF, reported on subjective measures, are weak in populations of patients with neurological disorders (Chaytor, Schmitter-Edgecombe, & Burr, 2006; Fuermaier et al., 2015). For instance, patients with PD who report complaints about EF do not necessarily show impairments on tests of EF and vice versa (Koerts, Van Beilen, Tucha, Leenders, & Brouwer, 2011; Koerts et al., 2012; Kudlicka, Clare, & Hindle, 2013; Lanni et al., 2014). One explanation for this weak association is that neuropsychological tests and questionnaires measure EF at different levels, because objective tests assess EF in a standardised environment and require patients to show an optimal performance, whereas questionnaires do not focus on performance, but ask for normal functioning in everyday life (Toplak, West, & Stanovich, 2013).

According to the World Health Organization's International Classification of Functioning, Disability and Health (ICF), (Heerkens et al., 2002), a disease can influence a patient's life on several hierarchical and interrelated levels: functional level (i.e. cognitive or physical impairments), daily life activity level, and participation level (i.e. involvement in societal domains such as work and mobility). In this context, QoL, defined as the subjective evaluation of various aspects (e.g. health or social functioning) of life in the context of one's needs and expectations, is an important concept (Kudlicka, Clare, & Hindle, 2014). Currently not much is known about the extent to which ICF levels and QoL are interrelated in PD; for example, to what extent do impairments in EF (i.e. functional level) have an influence on level of participation and QoL of patients? Therefore, this study aims to determine whether level of participation and QoL of patients with PD can be predicted by impairments at a functional level, as measured with both objective and subjective measures. It is expected that especially the combination of both objective and subjective measures, instead of using these approaches separately, will be of added value in predicting patients' level of participation and QoL.

# Methods

## Participants

Forty-two patients with idiopathic PD were included, who were diagnosed according to the UK Parkinson's Disease Brain Bank Criteria. Patients were recruited at the departments of neurology of three medical centres in the Netherlands. Patients were selected by a neurologist during regular consultation hours and were considered eligible for participation in this study when they reported problems in EF in daily life and had a mild disease severity (Hoehn and Yahr scale (H&Y), stage I-III). Severe neurological and psychiatric comorbidities, including dementia (i.e. SCOPA-COG: SCales for Outcomes in PArkinson's disease-COGnition score ≤17) (Verbaan et al., 2011) formed exclusion criteria. Disease severity was determined with the Unified Parkinson's Disease Rating Scale motor part (part-III) and H&Y. Patients in H&Y stage 4 and 5 were not included in this study. A Levodopa equivalent daily dose (LEDD) score (Esselink et al., 2004) was calculated for all patients receiving dopaminergic treatment. Five patients were not on dopaminergic treatment, two patients did not report medication use, and two received Deep Brain Stimulation (DBS) which was performed at least one year before study inclusion. Patients receiving dopaminergic treatment were assessed in the on phase. Furthermore, at the time of inclusion, 11 patients were employed (of which 5 patients had made adjustments to their work activities or hours) and 31 patients were unemployed, either because they reached the age of retirement (n=24) or they had decided to quit their jobs before retirement age because of their disease (n=7). With regard to the data that were collected from proxies, 2 patients were unable to find a life partner or relative willing to participate, one daughter of a patient participated, and the other 39 patients found their life partner willing to fill out questionnaires.

In addition, 94 healthy controls were included. No significant differences were found between groups with regard to age and level of education, but the groups did significantly differ in sex (table 1). This study obtained approval of a medical ethical committee in the Netherlands and was conducted in agreement with the Declaration of Helsinki. All participants signed an informed consent.

**Table 1. Descriptive and disease characteristics of patients with PD and healthy controls.**

| | PD (n=42) | | HC (n=94) | | | |
|---|---|---|---|---|---|---|
| | M (SD) | Range | M (SD) | Range | t/U/$X^2$ | *P* |
| Age in years | 60.8 (9.9) | 42 - 77 | 58.5 (6.8) | 38 - 84 | 1.31 | 0.197 |
| Education ǂ | 5.6 (1.1) | 3 - 7 | 5.3 (0.9) | 3 - 7 | 1663.50 | 0.082 |
| Gender ≠ | | | | | 3.98 | 0.046 |
| Male n (%) | 27 (64.3) | | 43 (45.7) | | | |
| Female n (%) | 15 (35.7) | | 51 (54.3) | | | |
| UPDRS III | 20.3 (9.5) | 8 - 59 | - | | | |
| H&Y | 2.1 (0.6) | 1 - 3 | - | | | |
| LEDD | 718.3 (622.3) | 0 - 3020.0 | - | | | |
| SCOPA-COG | 29.1 (4.5) | 19 - 37 | - | | | |
| HADS score | | | | | | |
| Anxiety | 6.7 (3.3) | 2 - 15 | 4.0 (2.7) | 0 - 12 | | |
| Depression | 6.1 (3.0) | 0 - 13 | 2.6 (2.6) | 0 - 11 | | |

*Note.* ǂMann-Whitney U test; ≠ $\chi^2$ test; PD=Parkinson's disease patients; HC=Healthy Controls, M=Mean; SD=Standard Deviation; Educational level was classified based on a 7-point scale; 1=<6 years primary school and 7=university degree; UPDRS motor part III=Unified Parkinson's Disease Rating Scale part III: range 0-108 max.; H&Y scale=Hoehn and Yahr scale: range 1-5; LEDD=Levodopa Equivalent Daily Dose; SCOPA-COG=SCales for Outcomes in PArkinson's Disease – COGnition; HADS=Hospital Anxiety and Depression Scale.

## Neuropsychological assessment

### *Procedure*

Before the neuropsychological assessment was administered, patients received the questionnaires at home. They were asked to fill them out and bring the questionnaires with them to their appointment. To minimise the chance that on-off fluctuations would occur during the neuropsychological assessment, patients were asked beforehand about their medication use and at what time they needed to take their medication. The test assistant reminded patients, if necessary, at these time points to take their medication to prevent them from going to an off phase, which affects cognitive performance. The time from taking dopaminergic medication to the start of the tests varied slightly; however, given that all patients were assessed at the same time in the morning at the neuropsychology departments of the respective hospitals and that patients usually take their first medication when they get up from bed, the time between intake of medication and start of the tests was minimised.

### *Objective measures of EF*

EF were assessed with the Trail Making Test (TMT) B/A ratio, Stroop Color-Word/Color card ratio, Visual Elevator Test total score (a subtest of the Test of Everyday Attention;

TEA); total score), Verbal Fluency Test: (total score of 3 letters) and Zoo Map (subtest of the Behavioural Assessment of the Dysexecutive Syndrome; BADS): total score.

### *Subjective measures of EF*

The Dysexecutive Questionnaire (DEX; total score) was used to assess problems in executive functioning in daily life. The "time management" scale of the Barkley Deficits in Executive Functioning Scale (BDEFS; total score) was used to measure patients' time management capacities. The scale also includes questions about taking initiative and distractibility, because these aspects can influence the time management capacities. The Brock Adaptive Functioning Questionnaire (BAFQ; mean total score of 12 scales) was used to measure cognitive and behavioural aspects of adaptive functioning. All questionnaires consisted of self-rating and proxy-rating versions (e.g. completed by the partner). Controls completed only self-rating versions of the questionnaires. On all questionnaires, higher scores represent more complaints.



### *Level of participation and QoL*

The Impact on Participation and Autonomy (IPA) scale (total score on the subscales "activities in or around the house" and "social relations") was used to assess patients' level of participation. Health-related QoL was measured with the Parkinson's Disease Questionnaire-39 (PDQ-39; total score). On both questionnaires higher scores represent lower levels of participation or QoL.

### *Anxiety and depression*

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS; total score and separate scores anxiety and depression subscales).

## Statistical analyses

Analyses of covariance were conducted to compare the groups on neuropsychological test measures and questionnaires of EF. Because patients showed significantly higher scores on both subscales of the HADS and more men were included in the patient group (anxiety subscale: t=4.67, $p$<0.001; depression subscale: t=6.87, $p$<0.001) (see table 1), HADS scores and sex were included as covariates. Test performances of all participants were also analysed from a clinical perspective, that is test scores were compared with normative data and considered as being "impaired" when a score fell within the lowest 10% of the normative sample (Lezak et al., 2004). Paired-samples t-tests were used to compare evaluations of patients and their relatives on

questionnaires of EF. Furthermore, effect sizes (Cohen's d*)* were calculated. Associations between objective and subjective measures of EF and measures of participation and QoL were analysed using Pearson's correlations within the patient group. Finally, two multiple regression analyses (method: enter) were used to determine whether objective and subjective measures can predict level of participation (dependent variable: IPA scale) and QoL (dependent variable: PDQ-39) in patients. To reduce the number of independent variables, the objective and subjective measure of EF showing the highest mean correlation with the dependent variables (i.e. IPA scale and PDQ-39) were included in the model. Moreover, the descriptive variables age, sex, UPDRS part III total score, and HADS total score (sum score of anxiety and depression subscales) were included as predictors. Statistical significance was reached at $\alpha<.05$. In case of multiple comparisons, a Bonferroni correction was applied.

# Results

## Performance on objective measures

Patients with PD performed significantly worse than controls on the Visual Elevator Test, when corrected for sex and HADS scores (table 2). No significant differences were found between groups on the other test measures of EF, which is consistent with the marginal to medium effect sizes. However, from a clinical perspective, patients showed a significantly higher percentage of impaired performances than did controls on 3 of 5 neuropsychological tests (TMT B/A ratio: $\chi^2$=7.61, *p*=0.006; Visual Elevator Test: $\chi^2$= 4.09, *p*=0.043; BADS Zoo Map subtest: $\chi^2$=6.33, *p*=0.012).

## Performance on subjective measures

Patients with PD reported significantly more problems in EF on the DEX, BAFQ, and BDEFS-time management questionnaires than did controls, which is consistent with the large effect sizes (see table 2). Comparison of patients' evaluations with those of their relatives showed that patients reported significantly more complaints on the BDEFS-time management questionnaire (table 3). Differences between patients and relatives on the other questionnaires were not significant. Furthermore, all subjective measures of EF were moderately to strongly interrelated (DEX and BDEFS-time management: r=0.45, *p*=0.004; DEX and BAFQ: r=0.79, *p*<0.001; BDEFS-time management and BAFQ: r=0.57, *p*<0.001).

**Table 2. Performance of patients with PD and healthy controls on objective and subjective measures of EF.**

| | PD (n=42) | | | HC (n=94) | | | comparison between groups | | ANCOVA | | Sign. covariates | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | (SD) | % ≤10th pc (n) | M | (SD) | % ≤10th pc (n) | $X^2$ | *p* | F | *p* | Sex | HADS anx | HADS dep | ES |
| Objective measures | | | | | | | | | | | | | | |
| TMT B/A | 2.60 | (1.01) | 23.81 (10) | 2.16 | (0.55) | 5.56 (5) | 7.61 | 0.006* | 5.52 | 0.020 | n.s. | n.s. | n.s. | 0.60 |
| Stroop 3/2 | 1.63 | (0.28) | 4.76 (2) | 1.55 | (0.19) | 0.00 (0) | | | 2.18 | 0.144 | n.s. | n.s. | n.s. | 0.35 |
| Visual elevator | 7.56 | (2.22) | 20.51 (8) | 8.51 | (1.63) | 7.95 (7) | 4.09 | 0.043* | 7.70 | 0.006** | n.s. | n.s. | * | 0.52 |
| Verbal fluency | 38.69 | (11.76) | 16.67 (7) | 39.88 | (11.74) | 12.77 (12) | | | 0.59 | 0.443 | n.s. | n.s. | n.s. | 0.10 |
| BADS Zoo map | 8.64 | (5.01) | 38.10 (16) | 10.26 | (5.21) | 18.09 (17) | 6.33 | 0.012* | 3.83 | 0.053 | n.s. | n.s. | n.s. | 0.31 |
| Subjective measures | | | | | | | | | | | | | | |
| DEX | 25.83 | (11.09) | - | 14.91 | (8.03) | | | | 9.57 | 0.002** | n.s. | * | n.s. | 1.20 |
| BAFQ | 2.25 | (0.42) | - | 1.79 | (0.37) | | | | 7.34 | 0.008** | * | * | n.s. | 1.18 |
| BDEFS | 45.18 | (12.07) | - | 29.77 | (6.27) | | | | 22.52 | <0.001** | n.s. | * | n.s. | 1.54 |

*Note*.PD=Parkinson's disease; HC=Healthy Controls, ANCOVA=Analysis of Covariance; sign=significant; M=Mean; SD=Standard Deviation; pc=percentile; anx=anxiety; dep=depression; ES=Effect Size; TMT B/A = Trail Making Test B/A ratio; Stroop 3/2 ratio = Stroop Color-Word/Color card ratio; BADS Zoo map = Behavioural Assessment of the Dysexecutive Syndrome Zoo map subtest; DEX = Dysexecutive Questionnaire; BAFQ = Brock Adaptive Functioning Questionnaire; BDEFS = Barkley Deficits in Executive Functioning Scale – time management scale; Comparison between groups on % impairments; *p-value <0.05; ** Significant p-value < Bonferroni corrected alpha.

**Table 3. Scores on questionnaires of patients with PD and their relatives (proxy-rating).**

| | Self-rating (n=42) | Proxy-rating (n=41) | Paired samples t-test | | Effect size |
|---|---|---|---|---|---|
| | M (SD) | M (SD) | t | p | d |
| DEX | 26.29 (10.82) | 22.02 (13.59) | 2.18 | 0.035 | 0.35 |
| BAFQ | 2.26 (0.39) | 0.51 (0.51) | 2.33 | 0.026 | 0.31 |
| BDEFS | 45.21 (12.24) | 40.29 (14.96) | 2.82 | 0.008* | 0.36 |

*Note.* PD=Parkinson's disease; M=Mean; SD=Standard Deviation; DEX=Dysexecutive Questionnaire; BAFQ=Brock Adaptive Functioning Questionnaire; BDEFS=Barkley Deficits in Executive Functioning Scale – time management scale; *$p$ < Bonferroni corrected alpha.

## Association between objective and subjective measures of EF

No significant correlations were found between any of the performances on the objective and subjective measures of EF (table 4).

## Contribution of objective and subjective measures of EF to level of participation and QoL

Within the patient group, no significant correlations were found between the objective test measures and the IPA scale and PDQ-39. The subjective measures DEX, BDEFS and BAFQ, however, were all significantly related to the PDQ-39 (see table 4). Furthermore, the scores on the IPA were significantly associated with the scores on the BDEFS- time management and BAFQ (see table 4). For subsequent regression analyses, the objective and subjective measures that showed the highest mean correlation with the dependent variables (i.e. IPA and PDQ-39) were included as independent variables (i.e. BADS Zoo Map subtest and BAFQ) in the model (see table 4 ).

The regression model explained 78% of variance of the total score on the IPA scale (F=7.06, $p$<0.001). Age, sex, Zoo Map total score, and BAFQ total score were significant predictors (table 5). Hence, for patients with PD a combination of a higher age, being female, a better Zoo Map score, but more complaints as measured using the BAFQ were related to a higher IPA scale score (i.e. a lower level of participation). For the PDQ-39, the results showed that the model explained 68% of variance (F=4.13, $p$=0.004). Significant predictors were sex, UPDRS part III total score, and BAFQ score (see table 5). Hence, the combination of being female, showing more severe PD related motor symptoms, and reporting more problems on the BAFQ was related to a higher score on the PDQ-39 (i.e. a reduced QoL) in patients with PD.

**Table 4. Pearson's correlations between objective and subjective measures of EF and measures of participation and QoL.**

| | DEX | *p* | Bdefs | *p* | BAFQ | *p* | IPA | *p* | PDQ-39 | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| Objective | | | | | | | | | | |
| TMT B/A | -0.03 | 0.856 | 0.20 | 0.222 | 0.14 | 0.381 | 0.17 | 0.314 | -0.04 | 0.793 |
| Stroop 3/2 | -0.32 | 0.042 | -0.22 | 0.185 | -0.30 | 0.062 | -0.04 | 0.825 | -0.09 | 0.566 |
| Visual elevator | -0.04 | 0.804 | -0.08 | 0.623 | -0.05 | 0.781 | -0.03 | 0.880 | -0.15 | 0.361 |
| Verbal fluency | 0.02 | 0.908 | 0.07 | 0.692 | -0.18 | 0.280 | 0.04 | 0.834 | 0.03 | 0.878 |
| BADS Zoo Map | 0.23 | 0.140 | 0.15 | 0.368 | 0.15 | 0.350 | 0.34 | 0.033 | -0.18 | 0.262 |
| Subjective | | | | | | | | | | |
| DEX | | | | | | | 0.32 | 0.045 | 0.39 | 0.011* |
| Bdefs | | | | | | | 0.42 | 0.007* | 0.47 | 0.003* |
| BAFQ | | | | | | | 0.51 | 0.002* | 0.42 | 0.008* |

*Note.* TMT B/A = Trail Making Test B/A ratio; Stroop 3/2 ratio = Stroop Color-Word/Color card ratio; BADS Zoo map = Behavioural Assessment of the Dysexecutive Syndrome Zoo map subtest; DEX = Dysexecutive Questionnaire; BAFQ = Brock Adaptive Functioning Questionnaire; BDEFS = Barkley Deficits in Executive Functioning Scale – time management scale; IPA = Impact on Participation and Autonomy, PDQ-39 = Parkinson's Disease Questionnaire-39; *Significant *p*-value < Bonferroni corrected alpha.

**Table 5. Results of the multiple regression analyses for the prediction of level of participation (IPA) and QoL (PDQ-39) in patients with PD.**

| | B | β | t | *p* |
|---|---|---|---|---|
| IPA | | | | |
| Constant | -30.81 | | -3.28 | 0.003** |
| Age | 0.22 | 0.35 | 2.68 | 0.012* |
| Gender | 6.59 | 0.52 | 3.72 | 0.001** |
| UPDRS part III score | -0.01 | -0.02 | -0.16 | 0.874 |
| HADS total score | 0.01 | 0.01 | 0.07 | 0.944 |
| BADS Zoo Map total score | 0.46 | 0.37 | 2.92 | 0.007** |
| BAFQ | 10.81 | 0.73 | 3.61 | 0.001** |
| PDQ-39 | | | | |
| Constant | -40.42 | | -1.11 | 0.275 |
| Age | -0.16 | -0.08 | -0.52 | 0.606 |
| Gender | 18.63 | 0.43 | 2.72 | 0.011* |
| UPDRS part III score | 0.70 | 0.32 | 2.25 | 0.032* |
| HADS total score | 0.24 | 0.06 | 0.30 | 0.767 |
| BADS Zoo Map total score | -1.00 | -0.24 | -1.66 | 0.107 |
| BAFQ | 28.27 | 0.57 | 2.44 | 0.021* |

*Note.* IPA=The Impact on Participation and Autonomy; QoL=Quality of Life; PDQ-39=Parkinson's Disease Questionnaire-39; UPDRS = Unified Parkinson's Disease Rating Scale-part III; HADS = Hospital Anxiety and Depression Scale; BADS = Behavioural Assessment of the Dysexecutive Syndrome; BAFQ = Brock Adaptive Functioning Questionnaire; *$p$<0.05, **$p$<0.01.

# Discussion

The objective and subjective measures of EF are each good predictors of level of participation in daily life and QoL in patients with mild to moderate PD. Both types of measurement indicate that patients with PD show difficulties in EF, but without being significantly related to each other. On subjective measures, patients reported significantly more complaints than did healthy controls, which is in line with previous studies (Koerts et al., 2011; Koerts et al., 2012; Koster et al., 2015). Compared with relatives, patients reported more problems in executive functioning related to time management (BDEFS-time management). Because the BDEFS-time management questionnaire includes questions related to time management, initiation of behaviour and distractibility, this suggests that patients are bothered with time management issues, initiation difficulties, and feelings of distraction that are not (yet) observed by their relatives, a finding that is consistent with the study of Lanni et al. (2014). With regard to all the other EF questionnaires, no differences were found between self- and proxy ratings. Thus, patients and their relatives in general agree on the EF problems as experienced by patients in daily life. This has also been found in recent studies and supports the idea that patients with PD do not have impaired self-awareness, which is usually indicated by lower scores of patients compared to their relatives and thus underestimation of problems (Koerts et al., 2011; Koerts et al., 2012; Vlagsma et al., 2016).

With regard to objective neuropsychological tests, patients with PD showed a higher percentage of impairments than controls on 3 out of 5 tests of EF, which is consistent with the fact that impairments in EF occur in PD (Elgh et al., 2009; McKinlay et al., 2010; Muslimovic et al., 2005). However, when directly comparing patients with PD with healthy controls, patients with PD performed significantly worse only on the Visual Elevator Test, but not on other neuropsychological tests. In this context, a relatively mild group of patients with PD was included in the present study.

Notwithstanding these findings, we found no significant associations between objective and subjective measures of EF, replicating previous studies (Koerts et al., 2011; Koerts et al., 2012; Lanni et al., 2014; Rabin et al., 2006). Apparently, test results do not correspond to complaints about EF, indicating that objective and subjective assessments measure performance at different levels. A possible explanation for this discrepancy is that standard neuropsychological tests of EF have a limited ecological validity, because these tests are structured, are standardised, and have clearly defined start and endpoints that are not available in daily life. This argument cannot, however, explain the nonsignificant association between the Zoo Map score (BADS) and the scores on the other questionnaires, because the BADS is considered to have a relatively high ecological validity. A better explanation might be

that in addition to aspects of EF such as planning and monitoring of behaviour that are measured with neuropsychological tests, questionnaires measure behavioural and social-emotional aspects. For instance, self-initiation of behaviour, empathy, impulsive behaviour, and social monitoring are hard to objectify with neuropsychological tests, but can be assessed with questionnaires. Finally, the fact that both approaches measure EF at different levels might also be of influence; objective tests target patients' optimal performance, whereas questionnaires ask patients to give their view on normal functioning in daily life (Heerkens et al., 2002).

To determine to what extent objective and subjective assessments of EF can predict level of participation and QoL in patients with PD, regression analyses were conducted. The combination of a *higher age*, *being female*, *a better performance on an objective test of EF* (BADS Zoo Map subtest), and reporting *more complaints about EF* in daily life was related to a significant reduction in level of participation (within the domains of household activities and social relations). Higher age having a negative influence on patients' level of participation might be explained by aging usually involving a reduction of social relations and increase in health problems, which can hamper, for example, the performance of household activities.



In previous studies on sex in relation to participation and QoL, female patients with PD tend to report greater disability, a stronger reduction in social functioning and, a lower perceived QoL as compared with male patients (Behari, Srivastava, & Pandey, 2005; Heller, Dogan, Schulz, & Reetz, 2014), which is in line with our findings. Furthermore, our results show that EF were associated with patients' participation level. However, contrary to what might be expected, we found that a better performance of objectively measured impairments in EF was associated with a lower level of participation. Even though the contribution of the performance of the objective test of EF to the level of participation should be considered in the context of all other variables, there is no clear explanation for this finding. It could be that patients with a sufficient score on the BADS Zoo Map subtest (that is not indicative of impairment) have an intact self-awareness and therefore tend to notice more problems in daily life functioning, which, in turn, leads to a lower level of participation (Lezak, 1982); however, this finding might also be based on chance. Level of participation was also predicted by subjective complaints (BAFQ). Reported complaints about EF are thus related to a decreased participation in PD patients' daily life, which supports the conclusions of a previous study (Foster & Hershey, 2011).

The combination of being *female*, showing more severe *PD related motor symptoms,* and reporting more *complaints about EF* was associated with a reduced QoL in patients. Interestingly, disease severity appeared to be a significant predictor of QoL, which is in line with a previous study (Appleman, Stavitsky, & Cronin-Golomb, 2011), but it was not related to participation. In addition, just as for participation

level, sex differences and subjective complaints about EF were found to be significant predictors of QoL. It is not surprising that subjective complaints were a significant predictor of QoL, because these also reflect the burden associated with impairments in EF, which, in turn, will negatively influence the QoL of patients. This strengthens the idea that sex differences and subjective complaints about EF are important aspects that need to be taken into account when determining patients' level of participation and QoL.

## Study limitations

A limitation of the present study is that more severely affected patients with PD (i.e. H&Y stage 4 and 5) were not included. It could be that more severely affected patients show and report more or other EF impairments and that their level of participation and QoL are predicted by different aspects. Furthermore, the heterogeneity of the patient group with regard to treatment (i.e. dopaminergic treatment and DBS (n=2)) is a limitation. Regarding dopaminergic treatment, this is inherent to PD, and on ethical grounds it was not possible to adjust patients' medication for research purposes. Furthermore, recent literature states that there is no convincing evidence for the assumption that DBS leads to impairments in cognitive functioning (Mehanna, 2014). Given that patients with severe cognitive impairments were excluded, including two patients who underwent DBS most likely did not influence the results.

## Conclusions

Impairments in EF that patients with mild to moderate PD show during the objective assessment are not related to complaints about EF in daily life. Both objective and subjective measures can, however, predict patients' level of participation. In addition, subjective measures explained a significant part of QoL. These findings indicate that the objective and subjective approaches are not interchangeable and each has a unique contribution to the assessment of problems in executive functioning and to the prediction of participation and QoL of patients with PD. Moreover, sex differences need to be taken into account. On the basis of these findings, we suggest to include one or more objective and subjective measures of EF as a standard part of assessment in patients with PD so as to recognize even mild deficits in EF early and to allow offering patients early interventions for these problems. This may foster maintaining patients' level of participation in daily life and related QoL for a longer period, despite the progression of the disease.

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## Chapter 4

# Parkinson's patients' executive profile and goals they set for improvement: why is cognitive rehabilitation not common practice?

**Published as:** Vlagsma, T. T., Koerts, J., Fasotti, L., Tucha, O., Van Laar, T., Dijkstra, H., & Spikman, J. M. (2016). Parkinson's patients' executive profile and goals they set for improvement: Why is cognitive rehabilitation not common practice?. *Neuropsychological rehabilitation*, *26*(2), 216-235.

# Abstract

Impairments in executive functions (EF) are the core cognitive impairment in patients with Parkinson's disease (PD). Surprisingly, cognitive rehabilitation is not routinely offered to patients with PD. However, in patients with acquired brain injury (ABI), cognitive rehabilitation, in particular strategic executive training, is common practice and has been shown to be effective. In this study, we determined whether patients with PD have different needs and aims with regard to strategic executive training than ABI patients, and whether possible differences might be a reason for not offering this kind of cognitive rehabilitation programme to patients with PD. Patients' needs and aims were operationalised by individually set goals, which were classified into domains of EF and daily life. In addition, patients with PD and ABI were compared on their cognitive, in particular EF, profile. Overall, PD patients' goals and cognitive profile were similar to those of patients with ABI. Therefore, based on the findings of this study, there is no reason to assume that strategic executive training cannot be part of standard therapy in PD. However, when strategic executive training is applied in clinical practice, disease-specific characteristics need to be taken into account.

# Introduction

Cognitive impairments are frequently documented in patients with Parkinson's disease (PD). In particular impairments of executive functions (EF) are already present in mild to moderate stages of PD and can even be observed in newly diagnosed patients. Executive dysfunctions are therefore considered a core feature of cognitive impairment in PD (Kudlicka et al., 2011; McKinlay et al., 2010; Muslimovic et al., 2005). EF are those capacities that enable individuals to adapt to new situations and to develop and pursue life goals in a constructive and productive way (Burgess & Simons, 2005). Impairments in EF can thus lead to a decreased independence in daily life functioning.

Pharmacological treatment, in particular dopaminergic medication, is the standard therapy in patients with PD. The literature, however, shows inconsistent results regarding whether pharmacological treatment enhances or impairs executive functioning (Cools et al., 2001; Cools et al., 2003; Vale, 2008). Nevertheless, it is obvious that patients with PD on dopaminergic medication still suffer from impairments of EF which they also experience in daily life (Koerts et al., 2011; Koerts et al., 2012). However, in clinical practice, admittance to neuropsychological rehabilitation programmes is not yet part of standard therapy for patients with PD, despite the fact that these programmes have been shown to be effective in other patient groups with executive impairments (e.g. in patients with acquired brain injury) (Cicerone et al., 2011; Wilson, 2008). This is even more surprising given the fact that over the past few years several studies have been conducted that aimed to show the effectiveness of cognitive rehabilitation programmes in patients with PD (Edwards et al., 2013; Hindle, Petrelli, Clare, & Kalbe, 2013; Mohlman et al., 2010; Mohlman, Chazin, & Georgescu, 2011; Naismith, Mowszowski, Diamond, & Lewis, 2013; Nombela et al., 2011; Paris et al., 2011; Reuter, Mehnert, Sammer, Oechsner, & Engelhardt, 2012; Sammer, Reuter, Hullmann, Kaps, & Vaitl, 2006; Sinforiani, Banchieri, Zucchella, Pacchetti, & Sandrini, 2004). Overall, the results of these studies lead to the conclusion that cognitive rehabilitation is also a feasible and effective treatment option for patients with PD. Especially with regard to impairments of EF, one study (Reuter et al., 2012) demonstrated that a multifaceted rehabilitation programme consisting of strategy training alongside function and skill training, resulted in improvements in daily life functioning and quality of life of patients with PD.

Strategy training of EF aims to teach patients a top-down approach that can be adapted flexibly and applies to various executive problems that patients encounter in daily life situations, and therefore focuses on improving daily life functioning and quality of life of patients with PD (Spikman, J.M. & Fasotti, L., 2012). Cicerone et al.

(2011) concluded in their review that cognitive rehabilitation programmes involving strategy training have been proven to be the most effective approaches for improving EF impairments in patients with ABI, in whom impairments of EF are frequently found (Bouwens, van Heugten, & Verhey, 2009; Ertzgaard, Ward, Wissel, & Borg, 2011; Evans, 2012). For example, Spikman et al. (2010) showed that patients with ABI who received executive strategy training resumed their previous roles in daily life and accomplished their individual goals significantly better than patients who received computer training. Also, patients with ABI who received executive strategy training showed more improvement with regard to setting realistic goals, planning, initiative and regulation compared to patients who received computer training.

Since impairments of EF are common in PD and strategy training has proven effective in other patient groups with EF impairments, this raised the question why it is not yet common practice to offer strategy training to patients with PD. One of the reasons might be that therapists do not consider this as an appropriate treatment option because they believe that disease-specific characteristics, such as motor impairments, fatigue and the progressive, neurodegenerative nature of the disease, might hamper patients with PD to profit from profiting from these rehabilitation programmes. Another possibility is that, despite the fact that executive impairments are common in patients with PD, it might be that these patients want to accomplish different goals and show a substantially different cognitive, in particular EF profile than patients with ABI who are admitted to rehabilitation programmes. This might lead therapists to believe that cognitive rehabilitation is not a suitable option for patients with PD.

To increase insight into whether this latter possibility is legitimate, it was determined whether patients with PD have different individual needs and aims for cognitive rehabilitation than a heterogeneous group of patients with ABI, e.g., traumatic brain injury (TBI), stroke and other neurological conditions, who successfully completed a strategy training. If we find that there are no substantial differences between these two groups regarding these aspects, this might lower the threshold for offering strategy training to patients with PD. Patients' needs and aims were operationalised by individual goals that patients specified within the context of executive strategy training. In addition, to what extent patients with PD show a different cognitive, in particular EF, profile than patients with ABI was also examined. The heterogeneous group of patients with ABI was chosen as a control group since (1) impairments of EF belong to the core cognitive impairments in all these subgroups of patients with ABI and (2) because strategic executive training has already been shown to be effective in this mixed group of patients with ABI (Spikman et al., 2010).

# Methods

## Ethics statement

This study was approved by the medical ethical committee of the University Medical Centre Groningen, the Netherlands. All patients voluntarily agreed to participate by means of written informed consent and were treated according to the declaration of Helsinki.

## Patients

Original descriptions of rehabilitation goals were available for 73 patients with ABI who participated in the study of Spikman and colleagues (2010). These 73 patients with ABI (31 with TBI, 31 with stroke, and 11 with other neurological conditions, such as cerebral tumours and encephalitis) were included in order to re-analyse their data for the purpose of the current study. All patients had been treated in an outpatient rehabilitation centre. For a more detailed description of the ABI patients, please see Spikman et al. (2010).

In addition, 26 idiopathic patients with PD were included. These patients were either recruited in the Netherlands from the departments of neurology of the University Medical Centre Groningen, Maastricht University Medical Centre, or the hospital Nij Smellinghe in Drachten. Patients were diagnosed according to the UK Parkinson's Disease Brain Bank Criteria and were assessed while on regular dopaminergic medication. A levodopa equivalent daily dose (LEDD) was calculated for all patients with PD (Esselink et al., 2004). The severity of the motor symptoms of patients with PD was examined using the Unified Parkinson's Disease Rating Scale part three (Fahn & Elton, 1987) and the Hoehn and Yahr (H&Y) scale (Hoehn & Yahr, 1967). Patients in H&Y stage 4 (severe disability, still able to walk or stand unassisted) and stage 5 (wheelchair bound or bedridden unless aided) were not included. Patients with PD were significantly older than patients with ABI ($t = -8.30$, $p<0.001$). Groups did not differ with regard to gender ($\chi^2 = 0.07$, $p = 0.796$) or level of education (Mann-Whitney $U = 796.50$, $p = 0.208$). Table 1 shows descriptive variables and disease characteristics of both patient groups.

**Table 1. Means (*SDs*) of descriptive and disease characteristics of ABI (n=73) and PD (n=26) patients.**

| | Patients with ABI | | Patients with PD | |
|---|---|---|---|---|
| | M (SD) | range | M (SD) | Range |
| Age in years | 42.7 (13.9) | 17 - 65 | 62.0 (8.6) | 48 - 79 |
| Education | 5.0 (1.1) | 2 - 7 | 5.3 (1.3) | 2 - 7 |
| Sex M/F (%) | 47/26 (64.4/35.6) | - | 16/10 (61.5/38.5) | - |
| UPDRS, part III | - | - | 24.8 (11.4) | 10 - 59 |
| H&Y | - | - | 2.4 (0.4) | 1.5 - 3 |
| LEDD | - | - | 771.0 (400.8) | 160 - 1670 |

*Note.* Educational level was classified based on a 7-point scale; 1 ≤ 6 years primary school and 7=university degree. Severity of motor symptoms in PD was measured by the UPDRS motor part; range 0-108 max. H&Y = Hoehn and Yahr scale (range 0-5). LEDD = levodopa equivalent daily dose. UPDRS = Unified Parkinson's Disease Rating Scale. Please see Spikman et al. (2010) for a more detailed description of patients with ABI.

## Study design and procedure

Both patient groups were assessed within randomised controlled trials (RCT). In the study of Spikman et al. (2010), patients with ABI were included if they (1) had a minimal post-onset time of 3 months, (2) were aged between 17 and 70 years, (3) lived at home, (4) had a history of daily life problems related to impairments in EF reported by themselves or their proxies, (5) experienced these impairments as burdensome, and (6) were motivated to participate in a cognitive rehabilitation programme. Consistent with these criteria, patients with PD or their proxies had to complain about problems related to executive dysfunctioning in daily life, had to experience these problems as burdensome, and had to be motivated to take part in a cognitive rehabilitation programme. Neurological and severe psychiatric comorbidity were exclusion criteria in both groups. In addition, severe cognitive comorbidity (including screening for dementia) was an exclusion criterion in both groups. The other inclusion and exclusion criteria were checked during a semi-structured interview with the patient and his or her proxy and on the basis of patients' medical files.

Patients with ABI and PD who met the abovementioned criteria underwent an extensive neuropsychological assessment, which consisted of several neuropsychological tests and a questionnaire. Additional inclusion criteria were a standard age score on the Behavioural Assessment of the Dysexecutive Syndrome (Wilson et al., 1996a) categorised as "low average" or lower, or a discrepancy between this standard age score and premorbid IQ measured by the Dutch Groninger Intelligence Test short version (Luteijn & van der Ploeg, 1983) of 15 points, and standard scores of 2 or lower on the BADS Six Elements Test or Zoo Map subtests. A total score of at least 18 points on the Dysexecutive Questionnaire (Burgess, Wilson,

Evans, & Emslie, 1996) was a final inclusion criterion (Spikman et al., 2010). There is a more detailed description of these tests and questionnaire below. If patients showed impairments on these subjective and/or objective measures of EF, they were randomly assigned to the experimental or control rehabilitation group. In both conditions, patients were asked to set three individual rehabilitation goals. The current study only focuses on these rehabilitation goals.

Goal descriptions of patients with ABI were retrieved from original patient files. Of the patients with ABI, four had only two written goal descriptions in the original files and one had five goal descriptions all of which were included for analysis. All patients with PD specified three goals, which were also retrieved from their files.

## Neuropsychological measures of executive and general cognitive functions

The following neuropsychological tests and questionnaire were administered in order to describe the cognitive and EF profile of patients with ABI and PD.

### *Executive functions*

All subtests of the BADS (Wilson et al., 1996a) were administered. The sum of profile scores resulted in a standard age score and a related clinical classification. Results of the subtests Zoo Map (total score part 1) and Six Elements were further analysed in order to study planning behaviour. The ratio B/A in the Trail Making Test (Reitan, 1958) was used to measure cognitive flexibility. Patients' ability to inhibit responses was measured by means of the ratio Color-Word card/Word card of the Stroop Color Word Test (Stroop, 1935).

The total score of the DEX questionnaire (Burgess et al., 1996) was used to measure subjective complaints related to problems with executive functioning in daily life. This questionnaire was completed by patients and their proxies. The difference of scores (patient total score-proxy total score) was used as a measure of self-awareness (Spikman et al., 2013). In the case of three patients with ABI, a therapist instead of a partner or family member completed the proxy version of the DEX.

### *General cognitive functions*

The Rey Auditory Verbal Learning Test (Dutch version; RAVLT; (Deelman et al., 1980) was administered to study the immediate and delayed recall of unrelated verbal information. The total score of the Digit Span forward and backward of the Wechsler Adult Intelligence Scale (WAIS; (Wechsler, 1987) was used to evaluate short-term verbal memory. Psychomotor speed was measured with the Trail Making Test (TMT; (Reitan, 1958) part A and the Word card of the Stroop Color Word Test (Stroop, 1935).

## Goal classifications

In order to compare patients' aims and needs, we classified rehabilitation goals of patients with PD and ABI twice: first into domains of EF and subsequently into domains of daily life activities. The classification of EF was based on Ylvisaker's (1998) definition and contained the following EF domains; (1) Planning, (2) Regulation, (3) Time management, (4) Initiative, (5) Self-Awareness, (6) Other EF (i.e. a goal which was related to EF but could not be classified into one of the other domains) and (7) Other (i.e. a goal that was not related to EF at all). Regulation included self-monitoring, inhibiting irrelevant behaviours, and cognitive flexibility. The category "time management" was added to the original definition of Ylvisaker, based on literature supporting the idea that a conscious awareness or sense of time is required for goal-directed behaviour and is therefore a legitimate aspect of EF (Barkley, 2011). Table 2 presents a detailed description of the classification.

**Table 2. Classification of domains of executive functions.**

| Domains of EF | Definition |
|---|---|
| (1) Planning | Goals that are related to mental processes preceding the execution of a task. |
| (2) Regulation | Goals that apply to the actual process of execution of a task. |
| (3) Time management | Goals that are explicitly related to deficits in estimating time. |
| (4) Initiative | Goals that apply to motivating oneself to actually start activities and/or goals that are aiming for a positive change compared to the current level of activities, such as implementing more different activities or accomplishing certain activities more often. |
| (5) Self-awareness | Goals that are related to a lack of awareness associated with disease-specific deficits. |
| (6) General EF | Goals that contain 2 or more domains of EF. However, if it is explicitly stated which domain has most priority, than the goal can be classified into one of the former categories. |
| (7) Other | Goals that are not related to EF. |

The World Health Organization's International Classification of Functioning, Disability, and Health (2002) was used for defining a classification of basic functioning and daily life domains (Heerkens et al., 2002). This led to a classification consisting of the following domains: (1) Cognitive functioning (non-EF), (2) Executive functioning, (3) Physical functioning, (4) Mental functioning and emotion regulation, (5) Self-care, (6) Occupation and education, (7) Housekeeping and gardening, (8) Finances and administration, (9) Leisure and community life, (10) Mobility, (11) Social relations, and (12) Communication. Table 3 shows this classification system in more detail.

The classification systems were developed in several steps. Three independent raters (T.T.V., J.M.S and J.K) classified all rehabilitation goals into domains of EF and subsequently into domains of basic functioning and daily life during

a first classification round. Since the inter-rater reliability was not sufficient, adjustments were made to the definition of domains in both classifications, leading to the classification systems as shown in Tables 2 and 3. Subsequently, all goals were classified again, a process that resulted in reliable ratings. These final classification systems were used by a fourth independent rater (H.T.D.) to classify all rehabilitation goals again. The ratings of H.T.D. were reliable when compared to the ratings of T.T.V. (see below for information about the inter-rater reliability). The ratings of T.T.V. were eventually used for further analyses.

**Table 3. Classification of domains of basic functioning, daily life activities and participation.**

| Domains | Examples |
|---|---|
| 1) Cognitive functioning (non EF) | Memory, reaction speed, visual perception, information processing |
| 2) Executive functioning | Planning, regulation, initiative, attention |
| 3) Physical functioning | Fatigue, fitness, energy, motor functions |
| 4) Mental functioning and emotion regulation | Self-esteem, self-confidence, nervousness, specific emotions |
| 5) Self-care | Bathing, shaving, getting dressed, eating and drinking |
| 6) Occupation and education | Work-day planning, homework, teaching, organising files |
| 7) Housekeeping and gardening | Cleaning, cooking, mowing, repairs |
| 8) Finances and administration | Payments, overview income and expenses, use of ATM machine, sorting bills |
| 9) Leisure & community life | Hobbies, holiday, politics, religion |
| 10) Mobility | Driving, public transport, taxi, biking |
| 11) Social relations | Friends/acquaintances, family, partner/children, colleagues |
| 12) Communication | Conversations, phoning, reading, e-mailing |

## Statistical analyses

In order to assess the quality of the goal classifications, the inter-rater agreement of both classifications (EF and daily life domains) was calculated by using Cohen's Kappa. Furthermore, $\chi^2$ tests were performed to compare distributions of EF goals and daily life goals between patient groups. Because all statistical assumptions were met, the cognitive and EF profiles of patients with PD and ABI were compared using ANCOVAs. As patient groups differed significantly with regard to age, this variable was used as a covariate in the model. The alpha level of 0.05 was adjusted for multiple comparisons using the Bonferroni correction, resulting in an alpha level of 0.004. Furthermore, Cohen's d was calculated for all neuropsychological tests and questionnaire comparisons between patients with PD and ABI. An effect size of <0.2 was labelled as marginal, 0.2 as small, 0.5 as medium, and 0.8 as large (Cohen, 1992). Paired samples t-tests were used to compare ratings of patients with PD and ABI to ratings of their

proxies on the DEX questionnaire. Since the ABI group consisted of TBI patients, stroke patients, and patients with other neurological conditions, ratings of patients and proxies on the DEX questionnaire were also analysed for each subgroup independently with paired samples t-tests. Results of neuropsychological tests were also analysed from a clinical perspective. Therefore, test results of the RAVLT, Digit Span, and Trail Making Test were compared to normative data. Performances that fell within the lowest 10% of the normative samples were considered to be *impaired* (Lezak et al., 2004). The BADS total score was transformed in a standardised scaled age score, which can be interpreted as a clinical score ranging from *impaired, borderline, low-average, average, above average, high* to *very high*. These descriptive data are reported and compared between groups by means of percentages.

# Results

## Classifications: Inter-rater reliability

The classification of goals into domains of EF resulted in a Cohen's Kappa of 0.71. The agreement between raters regarding the classification of goals in domains of daily life functioning was 0.86. According to the classification proposed by Landis & Koch (1977), the inter-rater reliability or agreement between ratings ranged from substantial to almost perfect.

## Classifications of EF and daily life domains: Comparisons between patients with PD and ABI

The group of 73 patients with ABI formulated 217 goals and the group of 26 patients with PD specified a total of 78 goals. Figure 1 shows the classification of goals into domains of EF for both patient groups. The percentage of goals that were set on "Time management" was significantly higher in patients with PD than in patients with ABI ($\chi^2$ = 15.57, p<0.001), whereas patients with ABI set a significantly higher percentage of goals on cognitive domains that were not related to EF when compared to patients with PD ($\chi^2$ = 6.13, p = 0.013). Furthermore, in both groups the majority of goals were set on the "Regulation" domain, including goals related to self-monitoring, inhibition of irrelevant behaviours and cognitive flexibility. Patients with ABI came up with only two goals in the domain of "Self-awareness", whereas patients with PD set no goals at all in this domain. For patients with ABI, the top three domains of EF in which most goals were set, were, respectively "Regulation", "Initiative" and "Planning". For patients with PD the top three were: "Regulation", "Planning" and "Initiative".

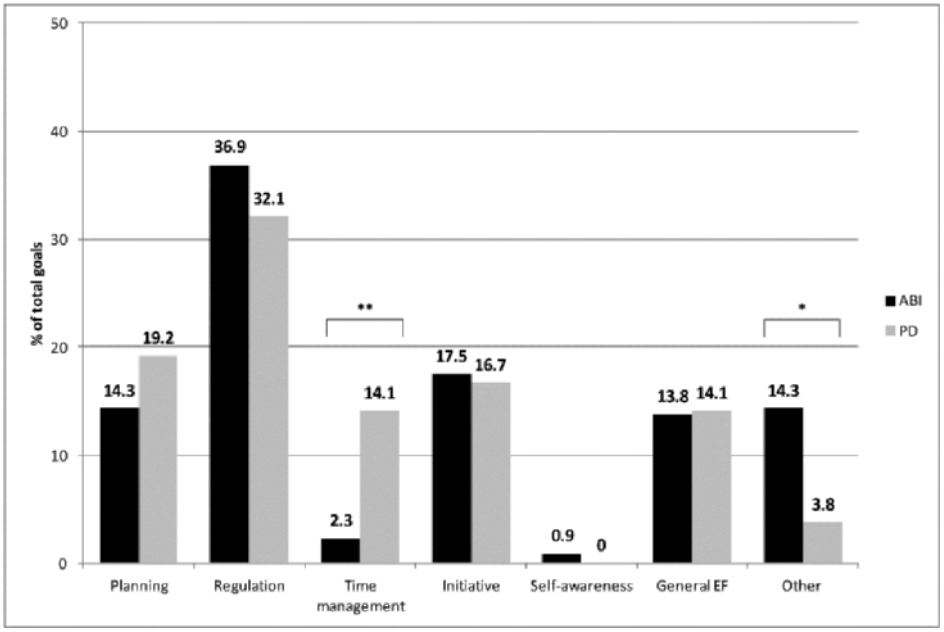


**Figure 1.** Rehabilitation goals of patients with PD and ABI classified into domains of EF (percentage of total number of goals set within patient groups). $\chi^2$ test: *p<.05, **p<0.01.



When goals were classified into domains of daily life, a significant difference was found between our patient groups for "Housekeeping and gardening" ($\chi^2$ = 12.95, p<0.001). Figure 2 shows that patients with PD set a considerable higher percentage of goals within this domain than did patients with ABI. There were no significant differences found between groups with regard to the other domains. The majority of goals of both patients with PD and ABI were classified in the domain of "Executive functions", indicating that these goals were not focused on specific daily life domains. Remarkably, none of patients with PD formulated goals that fell into the domain of "Physical functioning", whereas in patients with ABI the lowest number of goals was set on "Self-care". Patients with ABI set most goals within the following three domains: "Executive functioning", "Leisure and community life", "Social relations" and "Cognitive functioning" (in the latter two domains the same number of goals was formulated). For patients with PD, the top three were as follows: "Executive functioning", "Housekeeping and gardening" and "Communication".

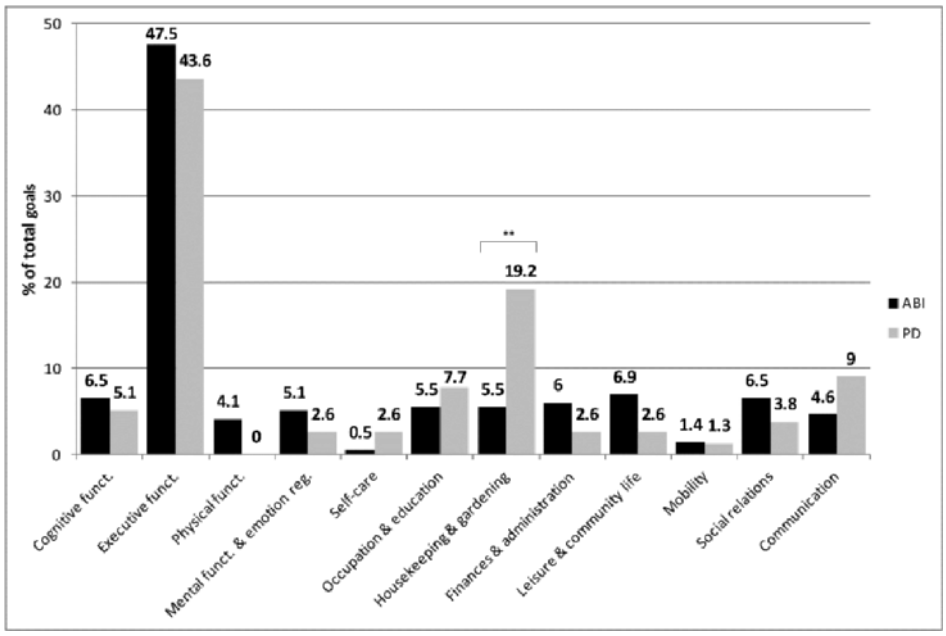


**Figure 2.** Rehabilitation goals of patients with PD and ABI classified into domains of basic cognitive functions and daily life activities and participation (percentage of total number of goals set within patient groups). $\chi^2$ test: **p<0.01.

## General cognitive and EF profile of patients with PD and ABI

Patients with PD and ABI showed only a minor difference in performance on tests of memory which did not reach significance (see Table 4). It was found that 42.3% of patients with PD and 43.8% of patients with ABI showed an impaired performance on the immediate recall of the RAVLT. The performance on the delayed recall of the RAVLT was labelled as clinically impaired in 3.9% of patients with PD in contrast to 13.7% of the ABI group. With regard to short-term verbal memory a higher percentage of patients with ABI were impaired when compared to patients with PD (respectively 26.4% and 11.5%). No differences were found between patient groups on measures of psychomotor speed (see Table 4), even though 26.9% of patients with PD were considered to be clinically impaired in psychomotor speed compared to more than half of patients with ABI (50.7%).

Likewise, no significant differences were found between patients with PD and ABI on several measures of EF, such as cognitive flexibility, inhibition and planning (see Table 4), which is consistent with the marginal to medium effect sizes. On the TMT ratio 28.0 % of patients with PD and 21.9% of patients with ABI were impaired on the TMT ratio. Also, the standardised age score of the BADS was labelled as “low average” or “impaired” in 30.8% of patients with PD compared to 42.5% of patients

with ABI. No significant differences were found between patients with PD and ABI regarding the number of problems with executive functioning in daily life as reported on the DEX questionnaire. Moreover, there was no significant difference between proxies of patients with PD and ABI with respect to the reported number of problems on the DEX questionnaire. When ratings for both groups of patients were compared to ratings of their proxies, no significant differences were found (paired samples t-test ABI: t = 0.49, p = 0.626; PD: t = 0.91, p = 0.374). The same was true when these ratings were independently compared for each subgroup of patients with ABI (TBI: t = -1.07, p = 0.294; stroke: t = 0.56, p = 0.580; other: t = -1.05, p = 0.317). Furthermore, there was no significant difference between patient groups when difference scores (DEX self–DEX proxy) of the DEX questionnaire were compared (see Table 4).

**Table 4. Performance of ABI and patients with PD on neuropsychological measures of general cognitive, executive functions and the DEX questionnaire.**

| | ABI (n=73) | | PD (n=26) | | ANCOVA | | Effect size |
|---|---|---|---|---|---|---|---|
| | M | (SD) | M | (SD) | F | *p* | *d* |
| Memory | | | | | | | |
| RAVLT IR | 39.72 | (10.61) | 35.00 | (10.08) | 0.20 | 0.657 | 0.45 |
| RAVLT DR | 8.00 | (3.37) | 7.65 | (2.83) | 0.19 | 0.662 | 0.11 |
| Digit Span total score | 13.26 | (3.65) | 14.65 | (3.11) | 3.61 | 0.060 | 0.40 |
| Psychomotor speed | | | | | | | |
| TMT A | 47.65 | (22.59) | 46.81 | (15.76) | 0.38 | 0.537 | 0.04 |
| Stroop Word card | 57.88 | (17.55) | 60.27 | (28.62) | 0.55 | 0.459 | 0.11 |
| Executive Functions | | | | | | | |
| TMT B/A ratio | 2.19 | (0.86) | 2.54 | (0.88) | 0.82 | 0.367 | 0.40 |
| Stroop ratio | 1.62 | (0.30) | 2.09 | (2.47) | 2.53 | 0.115 | 0.37 |
| BADS Zoo Map total score | 0.86 | (3.96) | -0.42 | (4.40) | 0.04 | 0.950 | 0.31 |
| BADS Six Elements | 5.05 | (1.35) | 5.40 | (1.08) | 0.42 | 0.516 | 0.27 |
| BADS Standardised age score | 89.21 | (13.64) | 94.00 | (15.45) | 0.67 | 0.417 | 0.34 |
| DEX Self | 31.37 | (13.00) | 25.46 | (9.88) | 1.64 | 0.203 | 0.48 |
| DEX Proxy | 32.11 | (14.66) | 23.35 | (11.73) | 1.82 | 0.181 | 0.63 |
| DEX Δ | -0.74 | (12.90) | 2.12 | (11.91) | 0.05 | 0.819 | 0.23 |

*Note.* ANCOVA = univariate analysis of covariance; IR = immediate recall score; DR = delayed recall score; TMT = Trailmaking test; BADS = Behavioural Assessment of the Dysexecutive Syndrome; Zoo map total score part 1; Significance $p < .004$, Bonferroni corrected alpha.

# Discussion

The results suggest that strategic executive training might be applied as a standard therapy for patients with PD, since their goals for cognitive rehabilitation of EF impairments, reflecting their needs and aims, as well as their EF profile are comparable to those of a mixed group of patients with ABI for whom strategic executive training has already been shown to be effective.

When patients' goals were classified into domains of EF, it was found that patients with PD and ABI set a comparable number of goals for the majority of EF domains (i.e. planning, regulation, initiative, self-awareness and general EF). Patients with PD did, however, set significantly more goals in the domain of "Time management" than patients with ABI. Since cognitive slowness is common in both patient groups (Broeders et al., 2013; Dikmen et al., 2009; Muslimovic et al., 2005; Rasquin et al., 2004; Spikman et al., 1996), it is more likely that this finding is due to slowness of movement (bradykinesia), the single most important diagnostic criterion of PD (Bloem et al., 2010). Patients with PD indeed frequently reported that they do not take their motor problems sufficiently into account and therefore need more time for activities than expected. From a neuro-anatomical perspective the fronto-striatal network plays a dominant role in time estimation. Evidence suggests that difficulties in time estimation in patients with PD are related to dysfunctions of this dopaminergic fronto-striatal network (Perbal-Hatif, 2012).

Patients with ABI set a significantly higher percentage of goals that was not related to EF at all than patients with PD. When analysing these goals in more detail, it was found that they were mainly related to problems in the regulation of social behaviour, including emotion perception, and to problems with regard to lowered self-esteem, memory, visuo-perception, and fatigue. However, since impairments in social cognition, memory, visuo-perception, and fatigue are also reported in patients with PD, the finding that patients with ABI set more goals related to these aspects than patients with PD is difficult to explain (Goldman, Weis, Stebbins, Bernard, & Goetz, 2012; Herrera, Cuetos, & Rodríguez-Ferreiro, 2011; McDonald, 2013; Millis et al., 2001; Ponsford et al., 2012; Solla et al., 2013; Spikman et al., 2013). Possibly, patients with ABI experience deficits in these domains as more restricting in daily life than do patients with PD.

Both patient groups set the smallest number of goals on "Self-awareness" and the largest number within the domain of "Regulation". This indicates that patients experience most problems when executing daily activities. Again, these findings underline the similarity between patients with PD and ABI concerning specific impairments of EF experienced as most restricting in daily life.

Patients' goals were also classified into the domains of basic functioning, daily life activities, and participation. The most important finding here is that in almost all domains (11 out of 12 domains), no significant differences between patients with PD and ABI were found. Both groups are thus highly comparable with regard to problems experienced in these three domains. Patients with PD only set a significantly higher number of goals within the domain of "Housekeeping and gardening" compared to patients with ABI, indicating that patients with PD experience more problems with EF when preparing and executing tasks around the house. A possible explanation for this finding is the fact that patients with PD were significantly older than patients with ABI and therefore a higher number of them had retired. This usually means that people spend more time at home. However, other explanations are also possible. By far, most goals of patients with PD and ABI were classified in the domain of "Executive functioning", which was defined as one of the basic functioning domains. This might indicate that problems with EF do not hinder patients in specific daily life domains, but have an impact on daily life functioning in general. This is in line with previous studies stating that impairments in EF exert a negative influence on everyday life and lead to an overall reduced level of participation (Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009; Perna, Loughan, & Talka, 2012).

It is worth noting that even though PD is characterised by motor symptoms, patients with PD did not set goals to improve their "Physical functioning". This is in line with the idea that patients with PD find cognitive impairments in daily life more restricting than motor impairments (Cahn et al., 1998; Klepac et al., 2008).

In addition to these comparisons, we performed a between groups comparison of specified goals falling into the top three domains of basic functioning, daily life activities, and participation. Results of this comparison showed that patients with ABI set more goals in domains that are related to "Social relations", "Leisure and community" activities, and "Cognitive functioning" than patients with PD. On the other hand, patients with PD set more goals related to "Household activities" and 'Communication'. It thus seems that patients with PD aim at improving activities they undertake (around the house), whereas patients with ABI intend to improve their (social) activities. However, the finding that patients with PD set more "Communication" goals could possibly also be explained as a disease-specific characteristic. Some studies have found problems with production and comprehension of language to be common in PD and to be related to impairments in EF (Colman et al., 2009; Colman, Koerts, Stowe, Leenders, & Bastiaanse, 2011).

With regard to comparisons on neuropsychological measures, it was found that general cognitive and in particular EF profiles of patients with PD and ABI are comparable. No significant differences between groups were found concerning their performances on neuropsychological tests for memory, psychomotor speed and EF, and the number of problems with EF experienced in daily life. When results were

interpreted from a clinical perspective, a large number of patients with PD as well as patients with ABI showed a clinically impaired performance (ranging from at least 20 to 67% for most target measures) with respect to memory, psychomotor speed, and EF. This is in agreement with results of previously conducted studies (Elliott, 2003; Godefroy et al., 2010) and the fact that ABI and PD are characterised by a dysfunctioning of the (pre)frontal cortex due, respectively, to direct injury of brain tissue or a dopaminergic dysfunctioning of the fronto-striatal circuits. When comparing the ratings of patients and their proxies regarding the number of problems with EF in daily life, no significant difference was found between patients with ABI and their relatives. The same result was found in patients with PD and their relatives. The agreement between patients and their proxies can be interpreted as an indicator of intact self-awareness, since patients with impaired self-awareness tend to underestimate their impairments when compared to their proxies' perspective (Hart, Sherer, Whyte, Polansky, & Novack, 2004; Spikman & van der Naalt, 2010). In other words, EF impairments reported by patients with PD and ABI are reliable and must be taken seriously.

Even though results seem promising with regard to introducing strategic executive training as standard therapy, the study is also marked by a number of shortcomings. One limitation is that we were not able to retrieve information regarding the underlying pathology and severity of patients with ABI. This was because patients were recruited from an outpatient rehabilitation setting and that in the majority of cases their hospital files were not obtainable. A second limitation of this study was that the group of patients with PD was relatively small. The calculated effect sizes for the differences in performance on neuropsychological tests, however, ranged from small to medium, indicating that a larger sample size of patients with PD would not have resulted in different conclusions. Moreover, when analysing differences regarding goals and cognitive profiles between patients with ABI and PD, disease severity within the group of patients with PD was not taken into account. This can be considered a limitation, since increasing disease severity possibly influences patients' goals and cognitive profiles. This would be an interesting question to answer in future studies. A final limitation of this study is the heterogeneity of the ABI group. Therefore a comparison between patients with PD and a group of patients with another neurodegenerative disease would have been desirable. However, according to our knowledge, strategic executive training is not offered to any other neurodegenerative patient group as standard therapy procedure. Moreover, in the context of the current study, this limitation can also be considered as a strength. Despite the great diversity of disease-specific characteristics within the group of patients with ABI, we still found that patients with PD were highly comparable to this group regarding their goals and the EF profile. This means that from a clinical

perspective the heterogeneity of the ABI group makes our conclusions even stronger than if we had only included a homogeneous TBI group.

In conclusion, based on our findings, we have no reason to assume that strategic executive training could not be offered as standard therapy to patients with PD. Results showed that patients with PD and ABI were not only comparable in terms of the rehabilitation goals they set, which reflect patients' needs and aims for cognitive rehabilitation, but were also comparable with regard to their cognitive and in particular EF profile. When considering the application of strategic executive training as standard therapy in patients with PD, neuropsychologists need to be aware, however, of disease-specific characteristics such as motor impairments and fatigue. In addition, for patients with PD the focus of strategic executive training should possibly be more on improving time management and functioning around the house. Future studies need to determine whether strategic executive training is actually effective in patients with PD, meaning that it results in improving patients' daily life functioning and quality of life. Furthermore, because of the neurodegenerative nature of PD, future studies should determine at which stage of the disease this treatment is suitable and for how long patients will benefit.

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## Chapter 5

# Cognitive rehabilitation in patients with Parkinson's disease: an overview

**Published as**: Vlagsma, T. T., & Spikman, J. M. (2014). Review: Neuropsychologische behandelingen voor patiënten met de ziekte van Parkinson. *Tijdschrift voor Neuropsychologie*, *9*(2), 128-43.

# Abstract

In this review we included nine studies (2004-2013) that investigated cognitive rehabilitation in patients with Parkinson's disease (PD), with a focus on improvement of executive functions (EF) as a result of the cognitive treatment protocols described. Of each individual cognitive treatment protocol the methodological criteria and effectiveness were evaluated. Consequently, all cognitive treatment protocols were classified based on the operational level of treatment that had been applied: function training, skills training and/or strategy training. Furthermore, the outcome measures that had been chosen were classified into three ICF levels: function level, activity/participation level and psychosocial level. Our findings show that the studies conducted so far lead to an improvement of cognitive functions on neuropsychological tests only. No transfer of training to daily life has been studied nor found. Furthermore, we found that the majority of included studies are of good methodological quality. Remarkably, most cognitive treatment protocols were limited to applying function training and measuring effect at function level. Given that impairments in EF can be considered central in PD, very little studies specifically aimed to improve executive functioning. Based on the current review, cognitive treatment protocols are proven to be feasible and beneficial for patients with PD, but there is a need for developing treatment protocols for executive problems that have impact on everyday life functioning, that is societal participation and quality of life (QoL).

# Introduction

Cognitive dysfunctions are reported in patients with PD in a variety of domains, such as attention, memory, visual-spatial functions and executive functions (EF) (Zgaljardic et al., 2003). Impairments in EF are predominant and can already be present in the early stages of PD (Kudlicka et al., 2011). EF are required for independent functioning in everyday life, since these functions enable us to set and achieve realistic life goals and to anticipate to unforeseen circumstances (Burgess & Simons, 2005). Therefore, impairments in EF have a negative influence on PD patients' everyday life functioning and quality of life (QoL) (Kudlicka et al., 2014).

Even though motor impairments are the core symptoms of PD, patients seem to experience cognitive impairments as even more restricting in everyday life functioning than motor symptoms (Klepac et al., 2008). Surprisingly, cognitive rehabilitation is not yet part of standard therapy for patients with PD. This raises the question to what extent effects of cognitive rehabilitation in PD have been studied so far. Therefore the current study gives an overview of the studies that have been conducted to investigate the effectiveness of cognitive rehabilitation in patients with PD. Specific attention will be given to whether these protocols addressed impairments in EF.

For each study that we included the methodological quality (e.g. the use of randomisation, control groups and sample sizes), type of training and the type of outcome measures were evaluated. Cognitive treatment protocols can be categorised as protocols based on function training, skills training or strategy training (Spikman & Fasotti, 2012).

Function training aims at improving cognitive impairments by stimulating the underlying cognitive functions. Repeated, mostly computer based, execution of tasks addressing this specific cognitive function is the key element of function training. The advantage of function training is that these protocols are basically self-supporting, implying that personal support by a therapist can be reduced to a minimum. This means that function training is a relatively low-cost form of cognitive rehabilitation. To date, however, the effect of function training in terms of improvement in everyday life functioning is still debated (van Heugten et al., 2016). Skills training aims to reduce the consequences of cognitive impairments in everyday life by practicing and improving the execution of specific everyday life activities in which patients experience these cognitive impairments. Strategy training aims to achieve the same goal by teaching patients cognitive strategies, which they can apply to those individual everyday life situations in which they experience cognitive impairments. The fundamental principle of strategy training is thus to help patients compensate for

their cognitive impairments in everyday life instead of restoring the cognitive functions itself.

The outcome measures that were used in the included studies were classified into different categories related to the levels of the International Classification of Functioning, Disability and Health (ICF): (1) function level: i.e. performance on neuropsychological tests, (2) activity/participation level: i.e. measures related to functioning in everyday life activities and participation in societal domains such as work, social relations, leisure activities and mobility, (3) personal aspects: measures related to well-being, mood, coping and QoL (WHO: Heerkens e.a., 2002). The primary aim of this review is to increase our insight into whether cognitive rehabilitation is feasible and effective for patients with PD and for which cognitive domains. We were specifically interested in cognitive treatment protocols that aim to improve executive functioning.

# Methods

The database PubMed was used to conduct a literature search on studies that evaluated cognitive treatment protocols in non-demented patients with PD. The following (combination of) search terms were used: “Parkinson’s disease” and “cognitive training”, “Parkinson’s disease” and “cognitive rehabilitation”, “Parkinson’s disease” and “training”, “Parkinson’s disease” and “executive rehabilitation”, “Parkinson’s disease” and “computer training”, “Parkinson’s disease” and “attention training” and “Parkinson’s disease” and “memory training”. Abstracts were included when they described studies that investigated the effectiveness of cognitive rehabilitation or training in patients with PD, including a baseline and post-treatment measurement. Abstracts were excluded when: 1) no cognitive treatment/training was described, 2) the described treatment/training focused on improving motor symptoms in patients with PD, 3) they concerned review studies, 4) cognitive treatment/training was investigated in other patient groups than PD and 5) they concerned theoretical studies on cognitive rehabilitation. The literature search resulted in 9 studies that were included. Subsequently, these studies were categorised following the methodological criteria of Cicerone e.a. (2000). Class I studies are of highest methodological quality and involve prospective, randomised controlled trials, Class II-studies are prospective cohort studies, retrospective studies, case-control studies or clinical series with well-designed controls, Class III studies were defined as clinical series without controls or case studies.

# Results

## Class I studies

So far, five Class I studies have been conducted on the effectiveness of cognitive rehabilitation in patients with PD (Table 1). Sammer et al. (2006) investigated the effectiveness of a function training aimed to improve EF. The training protocol consisted of repeated practise of neuropsychological tests of EF, such as the subtests 'Zoo map' and 'Key search' of the Behavioural Assessment of the Dysexecutive Syndrome (BADS). Furthermore, patients were asked to tell short stories in order to stimulate their speech production. The control treatment included occupational therapy, physiotherapy and physical treatment. Post-treatment, patients in the experimental condition showed a significant better performance on the subtests 'Ruleshift' and '6-Elements' of the BADS, which were not part of the training tasks, when compared to baseline. The control group did not show an improvement in test performance after treatment.

The study of Sammer et al. (2006) showed that function training for EF can lead to a better test performance on tests for EF in patients with PD. However, the outcome measures assessed only some specific aspects of EF and attention. Whether the function training also had an effect on other aspects of EF remains unclear. Moreover, the small sample sizes are considered a limitation of this study.

In 2011 París et al. performed a study on the effectiveness of function training on general cognitive functioning and QoL. The training consisted of computerised tasks for attention, (working) memory, speed of information processing, EF, visuospatial abilities and non-specific cognitive exercises (e.g. related to language and simple calculations). In addition, patients received 20 cognitive homework assignments weekly. These assignments are not described in detail in the paper. The control group received speech therapy in groups. When compared to the control group, patients who received the experimental treatment demonstrated significantly improved performance on at least one test of attention, information processing speed, memory, visuospatial and visuoconstructive abilities, semantic verbal fluency or EF. However, the experimental training showed no effect on measures of QoL, mood and cognitive problems in everyday life, indicating that this function training did not lead to improvement on the levels of personal aspects and activities/participation. Since París et al. (2011) do not describe the training tasks in detail, it is unclear which specific aspects of EF were trained. Another limitation of this study are the small sample sizes of patients with PD that were included.

Reuter et al. (2012) investigated a multimodal treatment protocol aimed to improve general cognitive functioning in PD. The experimental treatment included: (1)

function training: repeated practise of 'paper-and-pencil tasks' and computerised tasks mainly for EF and memory, (2) skill training for concentration, planning strategies, orientation and making use of mnemonics in everyday life activities, and (3) (psycho)motor training. The multimodal treatment protocol was compared to two control treatments: one control group received (1) function training and (2) skill/strategy training, whereas the other control group received only (1) function training. In addition, these control groups followed relaxation and vocational training to compensate for the extra time that was spend on training during the multimodal treatment. Patients and their relatives were instructed to continue practicing the exercises at home. When looking into more detail at patients' treatment goals, results showed that the majority of their goals focused on improving aspects of EF, which is in line with the assumption that patients with PD are hindered by impairments in EF in everyday life. Patients in the multimodal treatment group showed a significant greater improvement than both control groups on two screening measures of cognitive functioning (i.e. the Alzheimer Assessment Scale Cognition (ADAS) and Scales for Outcome of Parkinson's Disease Cognition (Scopa-Cog)) and on neuropsychological tests of EF. In addition, patients receiving the multimodal treatment reported a higher QoL post-treatment and achieved their treatment goals significantly more frequent than patients in the control groups. Furthermore, the multimodal treatment group developed a more active life style and reported to feel more confident when executing everyday life activities than the control groups. Also, a higher percentage of patients in the experimental group had continued exercising at home compared to the control groups. The treatment effects in favor of the multimodal treatment were still present at six months post-treatment. Based on these results, it can be concluded that the multimodal treatment showed positive effects on function level, as well as activity/participation level and level of personal aspects. The findings are robust given the large sample sizes that were included. A minor limitation related to the sample sizes is that the reason for the exclusion of 18 patients is not described.

The study of Edwards et al. (2013) evaluated the effectiveness and generalizability of a function training for speed of information processing. In addition, the authors were also interested in predictors of treatment success. The experimental treatment was a self-supporting computer training (called Insight) aimed to train speed of information processing in a visual realistic context. Patients had access to the computer training at home. The control group was formed by patients that were put on a waiting list receiving no treatment. Post-treatment both groups showed faster reaction times on a neuropsychological test for visual attention (Useful Field of View test, UFOV). In comparison with patients in the waiting-list-condition, the experimental group showed even greater improvement on this test in terms of faster reaction times. With regard to cognitive self-perception and depressive symptoms, no differences were found between baseline and post-treatment assessment. Thus, only

on function level a treatment effect was found. A longer disease duration, younger age at diagnosis and a higher Levodopa daily dose appeared to be predictors of treatment success. A limitation of this study is that measures of EF were not included, while the authors do suggest that improving speed of information processing might result in better executive functioning.

In a recent study of Naismith et al. (2013), a neuropsychological treatment was evaluated that aimed at improving patients' performance on neuropsychological tests for memory and cognitive functioning in general. The cognitive training consisted of two one-hour sessions: one hour psychoeducation related to PD followed by one hour of computer training (function level). Patients in a waiting list condition formed the control group. Results showed that the cognitive training group improved significantly more on a neuropsychological test for memory ('Logical memory', subtest of Wechsler Memory Scale-III) than patients in the waiting list condition. On tests for speed of information processing, cognitive flexibility and verbal fluency no differences between the groups were found. Unfortunately, the effect of psychoeducation on patients' knowledge about PD did not reach significance. Therefore, the effect of treatment was limited and only found on function level. Furthermore, it is hard to disentangle whether the improved performance on the memory test can be interpreted as an effect of the cognitive training only or can also (partly) be explained by an effect of psychoeducation. EF was not targeted specifically in the training and the outcome measures for EF showed no improvement post-treatment. Nevertheless, this is a valuable study since it is the first study that investigated and demonstrated the effectiveness of a memory training in patients with PD.

Overall, it is remarkable that all studies evaluated a treatment protocol that consisted at least partly of function training and that four out of five studies (París et al. (2010) did not define a primary outcome measure) also chose to use a primary outcome measure on function level (i.e. a neuropsychological test). This means that the evaluation of effectiveness was primarily focused on whether or not a cognitive treatment protocol leads to improved test performance. Three studies included also secondary outcome measures pertaining to functioning on activity level, participation and personal factors in addition to a primary outcome measure on function level. However, only Reuter et al. (2012) showed that the effect of treatment generalized to better functioning in everyday life. This study was also the only study that evaluated a cognitive treatment protocol which included skill training in addition to function training. This study concluded that function training alone did not lead to improvement in everyday life functioning, whereas the multimodal treatment did. Furthermore, the study of Reuter et al. was the only study that included a follow-up measurement. The other studies do not provide follow-up measurements that can lead to conclusions about the eventual long term effects of the evaluated cognitive treatment protocols, which can be considered a limitation.

**Table 1. Methodological ratings, descriptions and main findings of included studies.**

| Authors (year) *Class I/II/III* | PD N | H&Y | Controls N | M age (Sd) | Training content | Level cognitive training | Length of treatment |
|---|---|---|---|---|---|---|---|
| Sammer e.a. (2006) *Class I* | 12 | 2-3 | 14 PD | **Exp**. 70.8 (7.9) **Cont.** 68.5(9.0) | **Exp.:** Neuropsychological pencil-and-paper tasks and speech reproduction tasks **Cont.:** Occupational therapy, physiotherapy and physical treatment | Function training | 10 sessions of 30 min in 3-4 weeks |
| París e.a. (2011) *Class I* | 16 | 1-3 | 12 PD | **Exp.** 64.75 (9.19) **Cont**. 65.42 (9.60) | **Exp.:** Computer training and pencil-and-paper tasks: related to language or calculation skills **Cont.:** Speech therapy | Function training | 12 sessions of 45 min in 4 weeks |
| Reuter e.a. (2012) *Class I* | 222 | 2-4 | 71 PD 76 PD 75 PD | 64.0 (4.0) | **Exp.:** 1)Computer training and neuropsychological pencil-and-paper tasks. 2)Skills training 3)Psychomotor training **Cont. 1:** 1 and 2 **Cont. 2:** 1 | Function training Skills training | 1) 14 one-hour sessions, 4 per week 2) 10 sessions of 90min, 3 per week 3) 10-12 one-hour sessions at home: 1) 45 min, 3 per week 2)2 per week 3)2 per week |
| Edwards e.a. (2013) *Class I* | 32 | 1-3 | 42 PD | **Exp.** 69.38 (7.81) **Cont.** 68.17 (8.38) | **Exp.:** Computer training **Cont.:** Waiting list | Function training | min. 20 one-hour sessions, 3 per week |
| Naismith e.a. (2013) *Class I* | 35 | 1-3 | 15 PD | **Exp.** 68.5 (7.1) **Cont.** 64.9 (6.5) | **Exp.:** Computer training and psycho-education **Cont.:** Waiting list | Function training | 14 sessions of 2 hours, twice a week |

| Targets | Outcome measures | Level outcome measures | Measurements | Results |
|---|---|---|---|---|
| EF | BADS; Rule shift, 6-Elements test, TMT, FNL, AKT | **Primary:** Function | Baseline and post-treatment | The experimental group showed post-treatment a significant improved test performance on the 6-Elements and Rule-shift. The control group showed no significant improvements. With regard to working memory, attention and well-being, no effects of treatment nor differences between groups were found. |
| Attention, WM, SIP, memory, EF, visuospatial skills. QoL, mood and ADL | MMSE, ACE, WAIS-III; Digit Span, VLGT, SDMT, TMT, Stroop interference, WMS- III; Logical Memory I, II, CVLT-II, RBANS, Letter fluency, Semantic (animal)fluency, TOL, PDQ-39, GDS-15, CDS | Function Activity/ Participation Personal factors | Baseline and post-treatment | The experimental group showed post-treatment a significant better test performance that the control group on the Digit Span forward, Stroop interference, ROCFT, semantic fluency, TMT B and TOL. No differences were found on the PDQ-39, GDS-15 and CDS. |
| EF and everyday life functioning | **Primary:** ADAS-COG **Secondary:** SCOPA-COG, GAS, PASAT, BADS, MWT-B, PDQ-39, HADS | **Primary:** Function **Secondary:** Activity, participation and personal factors | Baseline, post-treatment and follow-up at 6 months | The experimental multimodal group showed post-treatment significant better performances on the primary and secondary outcome measures, compared to both control groups. A higher % of patients in the multimodal group continued their training at home and this group experienced a greater improvement of QoL than the control groups. These findings remained at follow-up. |
| Speed of information processing | **Primary:** UFOV **Secondary**: Cognitive Self-Report Questionnaire, CES-D | **Primary:** Function **Secondary:** Activity/participation and personal factors | Baseline and 3 months post-treatment | The experimental group performed post-treatment significantly better on the UFOV than controls. The control group performed post-treatment significantly better on the UFOV than at baseline. |
| Memory | **Primary:** WMS-III; Logical memory **Secondary:** TMT, Letter fluency, Psychoeducation questionnaire | **Primary**: Function **Secondary:** Function and personal factors | Baseline and post-treatment | Post-treatment the experimental group showed a significant better performance on the Logic memory test (learning and retention) than controls. On secondary outcome measures no differences were found. |

**Table 1 (continued). Methodological ratings, descriptions and main findings of included studies.**

| Authors (year) *Class I/II/III* | PD N | H&Y | Controls N | M age (Sd) | Training content | Level cognitive training | Length of treatment |
|---|---|---|---|---|---|---|---|
| Nombela e.a. (2011) II | 10 5 treated | 2-3 | 10 HC | **Exp.** 60.1 (3.04) **Untrained.** 61.2 (4.14) **Cont.** 59.6 (4.47) | **Exp.:** Pencil- and paper tasks: i.e. Sudoku puzzles. | Function training | 1 Sudoku a day during 6 months |
| Sinforiani e.a. (2004) *Class III* | 20 | 1,5 +/- 0,6 | - | 68.9 (7.1) | **Exp.:** Computertraining | Function training | 12 one-hour sessions, twice a week |
| Mohlman e.a. (2010) *Class III* | 1 | 2 | - | 74 | **Exp.:** everyday life activities and cognitive behavioural therapy | Function training | 10 sessions of 90-120 min |
| Mohlman e.a. (2011) *Class III* | 14 | - | - | 62.71 (7.32) | **Exp.:** everyday life activities | Function training | 4 sessions of 90 min, 1 per week |

*Note.* H&Y= Hoehn and Yahr scale for determining the severity of PD (range 0-5). Outcome measures; BADS= Behavioural Assessment of the Dysexecutive Syndrome; TMT: Trail Making Test; FNL: Face Name Learning Test; AKT: Alters Konzentrations Test; ADL: Activities of Daily Living; MMSE: Mini Mental State Examination; ACE: Addenbrooke Cognitive Examination; WAIS II: Wechsler Adult Intelligence Scale; CVLTII: California Verbal Learning Test; SDMT: Symbol Digit Modalities Test; WMS-III: Wechsler Memory Scale; ROCFT: Rey Osterrieth Complex Figure Test; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; TOL: Tower of London; PDQ-39: Parkinson's Disease Quality of Life Questionnaire; GDS-15: Geriatric Depression Scale; CDS: Cognitive Difficulties Scale;

| Targets | Outcome measures | Level outcome measures | Measurements | Results |
|---|---|---|---|---|
| Working memory and attention | Stroop; alternative version, Sudoku puzzles, FMRI | Function: including brain activity - fMRI | Baseline and post-treatment | The experimental group showed post-treatment significant better performances on the Stroop: reaction time↓, correct responses↑ and omissions ↓. Post-treatment, untrained patients needed more time to solve a Sudoku than the experimental group and controls. On FMRI the experimental group showed decreased cortical activation, which was comparable to the activation of healthy controls. |
| Attention, abstract reasoning, visual-spatial capacities | Babcock's story, Letter fluency, Raven's matrices, MMSE, WAIS-III; Digit Span, Corsi-test, WCST, Stroop | Function | Baseline, post-treatment and 6 months follow-up | At post-treatment patients performed significantly better on the Babcock's story, Letter fluency and Raven matrices compared to baseline. This finding remained at 6 months follow-up. On secondary measures no differences were found. |
| Executive skills and anxiety | PSWQ, BAI, STAI, HAM-A en D,BDI, Attention Control Scale, MMSE, Boston Naming Test, WAIS-III; Digit Span, Letter fluency, Stroop, TMT, WAIS-III; Similarities and Digit symbol | Personal factors and function | Baseline, second baseline at 1 month, post-treatment, follow-up at 1 and 3 months post-treatment | Post-treatment the patient reported a reduction of anxiety symptoms, which remained stable on the long term. With regard to test performance, no effect of treatment was found. |
| Executive skills | **Primary:** ATP practise log sheet: fatigue, effort, progress, enjoyment<br>**Secondary:** WAIS-III; Digit Span, Stroop, TMT, Letter fluency | **Primary:** Personal factors<br>**Secondary**: Function | Baseline and post-treatment. Primary outcome measure each session. | Patients experienced the training as feasible and enjoyable. Post-treatment patients reported a significant improvement in selective attention and switching of attention. Also a significant improvement was found compared to baseline on the Digit Span backwards, Stroop, TMT and COWAT. |

ADAS-COG: Alzheimer Assessment Scale Cognition; SCOPA-COG: Scales for Outcome of Parkinson's Disease-Cognition; GAS: Goal Attainment Scaling; PASAT: Paced Auditory Serial Addition Test; MWT-B: Mehrfach Wortschatz Test; HADS: Hospital Anxiety and Depression Scale; UFOV: Useful Field of View Test; CES-D: The Centre for Epidemiological Studies Depression Scale; fMRI: Functional Magnetic Resonance Imaging; WCST: Wisconsin Card Sorting Test; PSQW: Penn State Worry Questionnaire; BAI: Beck Anxiety Inventory; STAI: State-Trait Anxiety Inventory; HAM-A and D: Hamilton Scale for Anxiety and Depression; BDI: Beck Depression Inventory.

## Class II studies

Only one study could be classified as a Class II study (Table 1). Nombela et al. (2011) investigated whether a function training for working memory and attention would improve PD patients' performance on neuropsychological tests for working memory and attention and whether receiving training was related to patterns of functional brain activity, as measured with fMRI. Patients who received training were compared to a group of untrained patients and to a group of healthy controls. The cognitive training involved solving one Sudoku puzzle per day, during six months. Once a week a psychologist checked these puzzles and made corrections if necessary, which were also explained to patients. At baseline and post-treatment a modified version of the Stroop test was administered to patients while they were in the fMRI scanner. Compared to healthy controls, patients with PD needed significantly more time to solve a Sudoku puzzle and showed a significant longer reaction time on the alternative version of the Stroop test at baseline. When post-treatment comparisons were made between untrained patients with PD, trained patients with PD and healthy controls, results showed that untrained patients needed significantly more time to solve a Sudoku puzzle than the other groups. Furthermore, the patients in the training group showed a significant reduction of cortical activation when compared to untrained patients, which was comparable to the patterns of activation observed in healthy controls. This study has a few limitations that need to be mentioned. First, the included sample sizes were very small and Nombela et al. (2011) do not describe how patients were allocated to the different conditions. Moreover, the function training was limited in the sense that it included only Sudoku puzzles. Furthermore, since one outcome measure on function level was used, the authors were not able to draw reliable conclusions about possible effects of training on the domains of working memory and attention in general or effects on everyday life functioning and QoL.

## Class III-studies

Three studies were classified as Class III-studies (Table 1). In the study of Sinforiani et al. (2004) a treatment protocol was evaluated that consisted of both cognitive and motor training. The cognitive training involved a computer training that aimed to improve prefrontal regulated cognitive functions, by training aspects of attention, logic reasoning and visuo-spatial capacities. Directly after treatment and at six months follow-up, patients showed a significant improved performance on the Babcock's story, Fonologic fluency and Raven's matrices (which are considered tests for frontal functions). The authors conclude that the combination of cognitive and motor training leads to improved cognitive functioning, in particular to improved frontal cognitive functions. However, a remark that must be made is that the cognitive training did not

involve training of EF, EF being frontally regulated functions. Also, there was no effect of training found on the Wisconsin Card Sorting Test (WCST), which is surprising since this is considered an EF test that is sensitive to frontal dysfunction. The small sample sizes and the lack of a control group are considered methodological shortcomings. Another limitation is that effects on the level of activities/participation and personal factors were not studied, because the training as well as the outcome measures only aimed at training and improvements on function level.

Mohlman et al. (2010) described a case study of a PD patient that followed a cognitive rehabilitation protocol aimed at reducing symptoms of anxiety and improving EF. Half of the training protocol included cognitive behavioural therapy (CBT) and the other half focused on function training in the form of Attention Process Training-II (APT-II). The APT-II is a self-supporting training that trains different aspects of attention and logic reasoning. It uses audio discs that instruct patients to repeatedly practise activities in their home environment that rely heavily on attentional processes (e.g. divided attention: talking on the phone while cooking). After treatment, the symptoms of anxiety were evidently reduced and remained stable over time. However, no significant effect of training was found in terms of improvement on neuropsychological test performance. This finding was explained by the fact that the patient showed already (above) average performances on the majority of tests at baseline and by the presence of ceiling effects for some tests, reducing the possibility of improving test performance. An advantage of the APT-II is that it comprises tasks that are trained in everyday life situations. On the other hand, given that the primary aim of this study was to improve EF, it is surprising that the APT-II as well as the outcome measures focus primarily on aspects of attention (function level). Ecologically valid outcome measures related to EF in everyday life or QoL were not included (e.g. Behavioural Assessment of the Dysexecutive Syndrome). Furthermore, there were some methodological limitations: only one questionnaire was administered twice at three months follow-up, there were no statistical analyses performed and since the training protocol comprised CBT as well as APT-II it is hard to distinguish to which of these training elements the reduction of anxiety symptoms can be attributed.

In another study of Mohlman et al. (2011) the feasibility and patients' acceptance of the APT-II training was studied into more detail. In this study Mohlman et al. defined EF as attentional control and self-monitoring of behaviour. APT training sessions were led by doctoral psychology students that were experienced in giving APT training. In addition patients made assignments at home. Results showed that patients with PD reported to experience the training as feasible and acceptable. With regard to aspects of attention, patients reported significantly more improvement on selective attention and switching of attention that on other attentional aspects. Furthermore, patients' performance on tests for EF improved after training. However,

given that the main goal of this study was to determine whether APT-II training is feasible for patients with PD, the results would have been statistically more robust when a control group had been included and a follow-up measurement had been carried out. Besides, the inclusion of ecological valid measures of EF could have added relevant information.

# Discussion

The current review shows that up until 2014 a relatively small number of studies have been conducted on the effectiveness of cognitive rehabilitation in PD. To our knowledge the first study dates from 2004 (Sinforiani et al., 2004). Given that the studies that were included in this review reported a low percentage of drop-outs, we tentatively conclude that cognitive treatment protocols seem to be feasible for patients with PD.

The reviewed studies were classified according to their methodological characteristics. The majority of these studies (five out of nine) was of good methodological quality. In these studies patients were randomly allocated to a treatment condition and a control group was included (i.e. control treatment or waiting list condition). However, except for one study (Reuter et al., 2012: n>200) the sample sizes were small. In two third of the studies, the sample sizes did not exceed a number of 20 patients, which indicates that significant results must be interpreted with caution. Another important limitation for the majority of studies was the lack of a follow-up measurement. Therefore, it remains unclear whether effects of treatment that are found, would have lasted over time. This would be relevant information for clinical practice but also from a societal perspective, since this can increase our insight into the cost-efficiency of treating patients with PD.

With regard to the content of the cognitive treatment protocols, it is remarkable that all studies included, aimed to improve cognitive functioning by using function training. Thus, cognitive functions were trained by repeated practise of 'paper-and-pencil tasks' and computerised tasks. Only Mohlman et al. (2010; 2011) explicitly made a translation to everyday life functioning by stimulating patients to train aspects of attention by executing specific tasks in their home environment. However, the content of this training protocol must still be considered as a function training, since it was limited to repeated practise of specific tasks. Only Reuter et al. (2012) evaluated a multimodal treatment that consisted of skill training in addition to function training.

Except for the study of Mohlman et al. (2010), all studies led to the conclusion that function training is effective in patients with PD, meaning that training resulted in improved performance on neuropsychological tests. Remarkably, the primary outcome measures for the majority of studies were limited to measures on

function level (i.e. neuropsychological tests), with the exception of the studies of Mohlman et al. where primary outcome measures aimed to reflect improved functioning related to personal factors. Only the studies of París et al. (2011), Reuter et al. (2012) and Edward et al. (2013) evaluated the effectiveness of a cognitive training protocol on patients' functioning in everyday life activities and on their level of participation. The multimodal treatment of Reuter et al. (2012) was the only treatment that resulted in improvements in everyday life functioning and QoL of patients with PD.

Only four studies aimed specifically at improving EF. However, when looking into detail at these treatment protocols, it is questionable whether these studies actually trained EF. For instance, patients in the studies of Mohlman et al. (2010;2011) received an attention training (APT-II) and París et al. (2011) did not clarify which specific aspects of EF were trained. Moreover, the outcome measures related to EF consisted of basic and standard tests of EF instead of more complex and ecologically valid tests such as the BADS. The other five studies focused on improving speed of information processing, memory, attention, abstract reasoning or visuo-spatial functions. Given that EF are predominantly impaired in PD, it is surprising that only four studies aimed specifically on improving executive functioning.

Based on the conducted studies on cognitive rehabilitation in PD so far, it can be concluded that cognitive treatment protocols are feasible for patients with PD. Also, findings show that cognitive rehabilitation is effective in terms of improving cognitive functioning in PD. However, the most important limitation is that the majority of treatment protocols included only function training and measured the effectiveness of a training protocol only on function level as well. Therefore, the effectiveness of cognitive treatment on everyday life functioning in patients with PD remains unclear. This would be a highly interesting question to answer, since PD is a neurodegenerative disease and leads to an increasing reduction of patients' independence in everyday life. For patients with traumatic brain injury or stroke, cognitive rehabilitation has already been found to be effective in improving everyday life functioning (Krasny-Pacini et al., 2014). Spikman et al. (2010) showed that patients who received a multimodal strategy training for dysfunctions in EF, resumed to a significantly higher extent their previous (i.e. prior to the TBI or stroke) roles in society (work, social relations, leisure and mobility) than patients who merely received a computer training. Finally, based on the current review it can be concluded that in future research more attention should be paid to cognitive treatment protocols specifically aimed to improve EF and to evaluating the effects of such treatments on activity/participation level and on the level of personal factors.

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## Chapter 6

# Effectiveness of ReSET; a strategic executive treatment for executive dysfunctioning in patients with Parkinson's disease

**Published as:** Vlagsma, T. T., Duits, A. A., Dijkstra, H. T., van Laar, T., & Spikman, J. M. (2018). Effectiveness of ReSET; a strategic executive treatment for executive dysfunctioning in patients with Parkinson's disease. *Neuropsychological rehabilitation*, 1-18.

# Abstract

In this multicentre randomised controlled trial (RCT), forty-three patients with Parkinson's disease (PD) were randomly allocated to either the experimental condition receiving cognitive rehabilitation including strategy training (ReSET; Strategic Executive Treatment, n=24) or to the control condition receiving computerised repetitive practise training for attention (Cogniplus, n=16). We expected that strategy training (ReSET) would be more effective than cognitive training (Cogniplus) in improving patients' everyday life executive functioning. Neuropsychological assessment was administered at baseline, at 2 weeks and 3-5 months post-treatment. Primary outcome measure was the Role Resumption List (RRL). Secondary outcome measures were treatment goal attainment (TGA), Dysexecutive Questionnaire (DEX), Parkinson's Disease Questionnaire (PDQ-39), Zarit Burden Interview (ZBI) and neuropsychological tests. No effects of treatment were found on the primary outcome measure and on neuropsychological tests, except for one test of attention. At two weeks and 3-5 months post-treatment, patients with PD in both the ReSET and Cogniplus group reported a significant improvement in everyday life executive functioning, as measured with TGA and the DEX-self, with an advantage for ReSET only shortly after treatment. Given these results and that patients with PD were able to adhere to these treatments despite their motor symptoms and fatigue (i.e. the drop-out rate was small), we conclude that both strategy training and cognitive training for impairments in EF might be beneficial and feasible for patients with PD.

# Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is characterised by motor symptoms. Impairments in cognitive domains such as attention, memory visuospatial functions and executive functions (EF) are also common in PD (Elgh et al., 2009; Muslimovic et al., 2005). In particular, impairments of executive functions (EF) are frequently found and can already be present in the early stages of the disease (Kudlicka et al., 2011; McKinlay et al., 2010).

EF are higher order functions that control more basic cognitive processes like attention or memory. EF is an umbrella term that incorporates several functions such as planning, regulation and initiation of behaviour, time management and self-awareness (Vlagsma et al., 2015; Ylvisaker, 1998). These functions enable us to behave in a goal-directed way in non-routine and complex everyday life tasks and to anticipate unforeseen circumstances. Previous studies have shown that impairments in EF can lead to reduced independence in everyday life functioning and to a lower quality of life (QoL) (Kudlicka et al., 2014; Lawson et al., 2014b).

In neurological populations other than PD, e.g. acquired brain injury (ABI), it is common practice to offer patients neuropsychological rehabilitation programmes for impairments in executive functioning (Krasny-Pacini et al., 2013). For patients with PD, neuropsychological rehabilitation is not part of standard therapy. This is surprising as the profile of executive dysfunctions and reported needs and aims regarding neuropsychological rehabilitation of patients with PD are comparable to patients with ABI (Vlagsma et al., 2015). Moreover, because patients with PD report that their impairments in EF are at least as restrictive as their motor symptoms (Klepac et al., 2008) and since they have to cope with these impairments for a large part of their life, neuropsychological rehabilitation for impairments in EF could be particularly valuable to maintain patients' independence in everyday life for as long as possible.

In the last decade an increasing number of studies were conducted on neuropsychological rehabilitation in PD. However, to date only four studies investigated the effectiveness of cognitive interventions that specifically aimed to improve impairments in EF in patients with PD (Mohlman et al., 2010; Mohlman et al., 2011; Reuter et al., 2012; Sammer et al., 2006). These studies focused primarily on cognitive training, which involves repetitive practise of (computerised) tasks aimed at enhancing underlying cognitive functions. Importantly, these studies unanimously concluded that cognitive training for deficits in EF is feasible and beneficial for patients with PD (Calleo et al., 2012). Another five RCT studies were conducted on cognitive training in PD. These more general studies targeted a broader range of cognitive functions including EF (Cerasa et al., 2014; Paris et al., 2011; Pena et al., 2014; Petrelli et al., 2014; Zimmermann et al., 2014). The results of these randomised

controlled trials showed that cognitive training led to an overall significant improvement of PD patients' performance on neuropsychological test measures for EF. However, no evidence was found for generalisation of improvement to patients' everyday life functioning (Calleo et al., 2012; Leung et al., 2015). In two recent studies of Pena et al. (2014) and Reuter et al. (2012) patients with PD received a skill training in addition to cognitive training. The skill training involved guided and repetitive practise of specific activities in everyday life. Only Reuter et al. (2012) included in addition to neuropsychological test measures, outcome measures that were related to functioning in everyday life. They found that after treatment, patients with PD had improved in terms of their QoL, functioning on treatment goals, self-confidence and employment of a more active life style. For patients with TBI, the use of cognitive rehabilitation programmes that are based on strategy training is highly recommended for improving impairments in EF in everyday life, whereas cognitive training solely based on repetitive practise is not (Cicerone et al., 2011). Strategy training aims at teaching patients cognitive strategies that help them compensate the cognitive impairments they encounter in their everyday life activities. A large number of studies found solid evidence for the effectiveness of such intervention programmes, even in the long term (Tate et al., 2014). For example, Spikman et al. (2010) showed effectiveness of EF strategy training that lasted at least 6 months post-treatment. They found that ABI patients who received strategy training resumed their previous roles in everyday life more often, showed more improvement with regard to setting and accomplishing realistic goals and showed better planning and regulation abilities than patients who received computerised cognitive training. However, patients in both groups showed no improvement on neuropsychological tests for EF or attention, which led the authors to conclude that although these tests may be sensitive to impairments, they are not sensitive to changes due to treatment. Recently, Foster and colleagues (2017) investigated the feasibility of an individualized cognitive strategy training in a case series of seven non-demented patients with PD. Patients evaluated this intervention as being acceptable and engaging, corroborating its feasibility. Although this study did not aim to evaluate the effectiveness of the intervention, patients also reported improvement on a scale for performance and satisfaction of everyday life tasks, which is promising. However, the cognitive targets for treatment were not specified in this study. Given that strategy training has a positive effect on indications of everyday life EF in ABI patients and the findings of the study of Foster et al. (2017) in patients with PD, it is surprising that the effect of strategy training on everyday life executive impairments has not yet been examined in patients with PD. Therefore, the main goal of the present study was to investigate the effectiveness of a cognitive rehabilitation programme based on strategy training (ReSET; Strategic Executive Treatment) on everyday life executive functioning, level of participation and QoL in patients with PD, both immediately after treatment and in the longer term. In a

RCT design we compared this cognitive rehabilitation programme based on strategy training to a computerised cognitive training for attention and working memory (Cogniplus). Attention and working memory are basic cognitive functions, which are also necessary when performing complex executive tasks. We hypothesise that Cogniplus may lead to improved performance on neuropsychological tests for aspects of EF, but will not translate into improved executive functioning in everyday life. This is in contrast to ReSET of which we expect that it will lead to improvement in everyday life executive functioning. A second goal was to investigate whether cognitive rehabilitation based on strategy training was feasible for patients with PD. When compared to ABI patients, motor impairments and fatigue might have a stronger negative impact on their abilities to follow out-patient treatment and to practise with assignments at home.

# Methods

## Study design and procedure

This study was conducted in three medical centres in the Netherlands: University Medical Centre Groningen (UMCG), Maastricht University Medical Centre (MUMC) and Nij Smellinghe Drachten. The study was approved by the ethics review board (ERB) of the UMCG and was conducted in accordance with the declaration of Helsinki.

Patients were eligible for participation in this study when they were aged between 18 and 80 years, diagnosed with PD according to the UK Parkinson's Disease Brain Bank Criteria and had a disease severity ≤ Hoehn & Yahr (H&Y: (Hoehn & Yahr, 1967)) stage 3, i.e. patients had to be mobile in order to visit one of the medical centres on a weekly basis for at least three months. Furthermore, patients had to be (1) motivated for treatment, (2) had to report problems with EF in everyday life they experienced as burdensome (based on semi-structured interview and/or a total score of ≥18 on the Dysexecutive Questionnaire (DEX: (Burgess et al., 1996)); and/or (3) had impairments on objective neuropsychological tests of EF. Impairments were defined as: a standard score of ≤2 on the subtests Zoo Map Test or Six Elements Test of the Behavioural Assessment of the Dysexecutive Syndrome (BADS: (Burgess et al., 1996)) and/or a standard age total score on the BADS categorised as 'low average" or lower and/or a discrepancy of 15 points between standard age score and premorbid IQ as measured with the short version of the Dutch Groninger Intelligence Test (Luteijn & van der Ploeg, 1983). Exclusion criteria were severe neurological and psychiatric comorbidity including dementia (i.e. SCales for Outcomes in PArkinson's disease-COGnition scale score ≤17 (Verbaan et al., 2011)). The above-mentioned tests and questionnaires were part of an extensive neuropsychological assessment. Results of

this assessment were used as the baseline measurement (T0) when patients were found to be eligible for participation in accordance with the inclusion criteria.

Eligible patients were randomly assigned to either the experimental (ReSET) or control (Cogniplus) treatment by drawing lots. In order to balance the allocation of patients to both treatment conditions, lots were drawn per 4 patients (i.e. 2 experimental and 2 control condition). A coworker who was not actively involved in the study was responsible for the drawing of lots.

Both ReSET and Cogniplus consisted of 14 one hour sessions; once a week or if possible twice a week. Patients were assessed with a neuropsychological test battery (i.e. interview, tests and questionnaires) at three time points: baseline (T0), 2 weeks post-treatment (T1) and 3-5 months after the last treatment session (T2). Well-trained test assistants, who were blind for the treatment condition, administered the tests.

## Participants

Forty-nine patients with PD were included (UMCG: n=33, MUMC: n=8,Nij Smellinghe: n=8). Six patients dropped out during the treatment period: 2 because of physical disabilities and 4 patients because of loss of motivation. Therefore, 43 patients (ReSET: n=24, Cogniplus: n=19) completed the treatment and post-treatment assessment (T1; Figure 1). Another 4 patients dropped out to 3-5 months post-treatment assessment (T2): one patient had developed severe psychiatric comorbidity, one patient stated after four sessions that he considered himself to be sufficiently improved as he had no complaints anymore and therefore felt no necessity to continue the treatment and 2 patients could not complete assessment because of logistic reasons. Thirty-nine patients thus completed the study protocol (Figure 1).

Disease severity was determined with the Unified Parkinson's Disease Rating Scale motor part (UPDRS-III) and H&Y scale. A Levodopa equivalent daily dose (LEDD; (Esselink et al., 2004)) score was calculated for all patients who were on dopaminergic treatment. Three patients were not on dopaminergic treatment, for 2 patients medication use was not reported and 4 patients received Deep Brain Stimulation (DBS) in addition to dopaminergic treatment. Surgery was performed at least one year prior to study inclusion. Patients on dopaminergic treatment were in the on phase during treatment and neuropsychological assessment. Table 1 presents descriptive variables and disease characteristics of both treatment groups. No differences were found between treatment groups regarding age, disease duration and disease severity.

Furthermore, a healthy control group (n=90) was included to determine whether the patients with PD showed impairments in EF at baseline compared to healthy controls. Table 2 shows that both groups were comparable as there were no differences with regard to age, gender, premorbid IQ and level of education. However, at baseline patients with PD reported significantly more symptoms of anxiety and depression on the Hospital Anxiety and Depression Scale (HADS:(Zigmond & Snaith, 1983) than healthy controls.

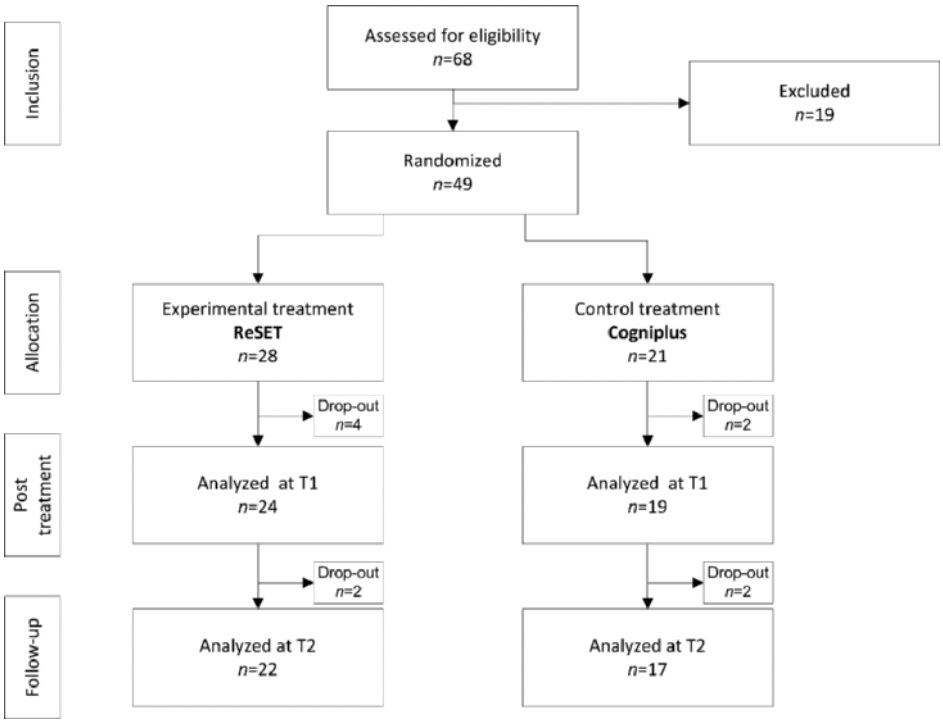


**Figure 1.** Flow chart of the inclusion process.

**Table 1. Descriptive and disease characteristics of patients with PD in both treatment groups.**

| | ReSET (n=24) | | Cogniplus (n=19) | | | |
|---|---|---|---|---|---|---|
| | M (SD) | Range | M (SD) | Range | $t/U/X^2$ | *p* |
| Descriptives | | | | | | |
| Age in years | 60.21 (10.42) | 42 - 74 | 62.58 (8.84) | 44 - 79 | -0.79 | 0.433 |
| Education[a] | 5.46 (1.32) | 2 - 7 | 5.58 (1.07) | 3 - 7 | 230.50 | 0.949 |
| IQ | 108.05 (6.32) | 92 - 121 | 105.47 (10.36) | 89 - 130 | 0.97 | 0.336 |
| Gender – male n (%)[b] | 14 (58) | | 13 (68) | | 0.46 | 0.497 |
| Disease characteristics | | | | | | |
| Disease duration in years | 6.02 (6.26) | 0.5 - 24 | 6.72 (4.97) | 1 - 15 | -0.39 | 0.703 |
| UPDRS-III | 23.96 (9.46) | 8 - 46 | 22.24 (11.44) | 11 - 59 | 0.52 | 0.606 |
| H&Y | 2.37 (0.57) | 1 - 3 | 2.19 (0.39) | 1.5 - 3 | 147.00 | 0.095 |
| LEDD | 727.50 (336.36) | 0 - 1230.00 | 652.50 (564.66) | 0 - 2080.00 | 0.53 | 0.600 |
| Global cognition & mood | | | | | | |
| SCOPA-COG | 28.29 (4.76) | 19 - 37 | 28.79 (4.70) | 19 - 37 | -0.34 | 0.734 |
| HADS - Anxiety | 6.17 (3.50) | 1 - 15 | 6.74 (3.68) | 2 - 14 | -0.52 | 0.607 |
| HADS - Depression | 5.83 (3.23) | 0 - 11 | 5.63 (3.27) | 1 - 12 | 0.2 | 0.841 |

*Note*. [a]Mann-Whitney U test; [b] $\chi^2$ test. Notes. educational level was classified based on a 7-point scale; 1=<6 years primary school and 7=university degree; IQ was measured with the short version of the Dutch Groninger Intelligence Scale; UPDRS motor part III= Unified Parkinson's Disease Rating Scale part III: range 0-108 max.; H&Y scale=Hoehn and Yahr scale: range 1-5; LEDD=Levodopa Equivalent Daily Dose; SCOPA-COG=SCales for Outcomes in PArkinson's Disease – COGnition; HADS=Hospital Anxiety and Depression Scale.

**Table 2. Descriptive characteristics of patients with PD and healthy controls.**

| | **PD** (n=43) | | **HC** (n=90) | | | |
|---|---|---|---|---|---|---|
| | **M (SD)** | **Range** | **M (SD)** | **Range** | **t/U/X²** | ***p*** |
| Age in years | 61.26 (9.72) | 42 - 79 | 58.97 (6.41) | 47 - 84 | 1.41 | 0.165 |
| Education[a] | 5.51 (1.20) | 2 - 7 | 5.32 (0.86) | 3 - 7 | 1657.50 | 0.154 |
| IQ | 106.85 (8.42) | 89 - 130 | 106.43 (8.48) | 86 - 130 | 0.27 | 0.790 |
| Gender - male n (%)[b] | 27 (63) | | 42 (47) | | 3.03 | 0.082 |
| **Neuropsychological tests** | | | | | | |
| EF | | | | | | |
| TMT B/A | 2.57 (0.96) | | 2.17 (0.54) | | 2.57 | 0.013 |
| Zoo-map total score | 6.95 (5.94) | | 10.24 (5.19) | | -3.25 | 0.001 |
| Attention | | | | | | |
| TMT A | 43.72 (13.79) | | 33.26 (9.29) | | 4.49 | <0.001 |
| **Questionnaires** | | | | | | |
| DEX self | 24.40 (10.64) | | 14.80 (7.93) | | 5.26 | <0.001 |
| HADS - Anxiety | 6.42 (3.55) | 1 - 15 | 3.85 (2.56) | 0 - 12 | 4.23 | <0.001 |
| HADS - Depression | 5.74 (3.21) | 0 - 12 | 2.62 (2.66) | 0 - 11 | 5.83 | <0.001 |

*Note.* [a]Mann-Whitney U test; [b] $\chi^2$ test. Notes: educational level was classified based on a 7-point scale; 1=<6 years primary school and 7=university degree; IQ was measured with the short version of the Dutch Groninger Intelligence Scale; TMT B/A = Trail Making Test B/A ratio; TEA = Test of Everyday Attention; TMT A = Trail Making Test A; DEX = Dysexecutive Questionnaire; HADS=Hospital Anxiety and Depression Scale.

## Experimental treatment ReSET: strategic executive treatment

ReSET is an individual treatment, given by experienced neuropsychologists. The aim is to improve or stabilise the level of independence and QoL, by teaching patients strategies to compensate for impairments in EF in everyday life situations. These strategies allow patients to tackle everyday life situations in a systematic and structured way, by formulating their intentions and actions explicitly in terms of goals and sub goals (planning) and effectively executing these plans, while monitoring their behaviour.

The content of the treatment protocol is based on the "Multifaceted treatment programme" of Spikman et al. (2010) and targets several aspects of EF as defined by Ylvisaker et al. (1998): self-awareness, goal setting, planning, initiation and monitoring of behaviour, flexibility and strategic behaviour. Adjustments were made to the protocol of Spikman et al. (2010) in order to make it more feasible for patients with PD. The number of sessions was reduced from 24 to 14. There were also fewer exercises per session as PD patients' psychomotor tempo is often reduced (Vlagsma et al., 2016).

The ReSET protocol consisted of 14 one-hour sessions that were grouped into three modules. The first module 'Information and awareness' consisted of three sessions aimed at increasing patients' insight into their executive dysfunctions and the consequences of these dysfunctions in everyday life. This was achieved by giving psycho-education to patients and their relatives and evaluating patients' strengths and weaknesses based on their performance on the neuropsychological assessment. In the third session, patients were asked to formulate three individual goals related to executive functioning that could be improved through the treatment (Vlagsma et al., 2015) and were asked to rate their level of functioning regarding these goals.

The second module 'Goal setting and planning' consisted of six sessions based on the General Planning Approach (GPA: Spikman et al., 2010). The GPA teaches patients to structure the planning and execution of activities by formulating a concrete goal and explicitly describing the actions that need to be carried out in order to achieve the goal in a step-by-step manner, the estimated time per action and the materials needed for accomplishing the goal. Furthermore, patients were taught to make a realistic and energy balanced day-to-day and week planning and learned to adjust their planning to their individual fluctuating energy level. Also they were taught how to use an organiser properly. Therapists' assistance was gradually reduced over sessions. Homework involved mostly the execution of activities that were planned during the session. The homework assignments were evaluated at the beginning of each session.

The third module 'Initiative, execution and regulation' consisted of five sessions. While in the second module the emphasis lay on the planning process, this

module focused more on the execution of the plan. During these sessions, Goal Management Training (GMT; (Levine et al., 2000) plays a central role in which patients are taught to build in a self-control mechanism that helps them to 'keep on track' and actually achieve their goals as planned. Furthermore, attention was given to making the initiation of a plan easier by using, external aids (e.g. organiser, alarm).

## Control treatment Cogniplus

The training protocol of Cogniplus (Schuhfried, 2007) consisted of 14 one-hour sessions. Within these sessions six subtests of the computer training program Cogniplus (Schuhfried, 2007)(Schuhfried, 2007) were individually administered to patients. Five subtests aimed at training aspects of attention (i.e. alertness, selective attention, divided attention and vigilance) and one subtest aimed at training working memory. For the rest of this paper, the control treatment is referred to as 'Cogniplus'. The program is basically self-supporting; however, a psychological test assistant was present to provide technical support if necessary. Each aspect of attention and working memory was trained with a separate task. During each session, patients performed three different tasks and trained different aspects of attention and working memory. This ensured that sessions remained challenging. Patients who received the computer training were also asked to formulate three individual executive goals during the third session and were asked to rate their level of functioning regarding their goals at baseline and post-treatment assessments.

## Measures

All measures were administered at baseline, 2 weeks and 3-5months post-treatment, with exception of the Rey Auditory Learning Test (RAVLT: (Deelman, Brouwer, van Zomeren, & Saan, 1980)), which was only used at baseline.



### *Primary outcome measure*

**INTERVIEW**

The Role Resumption list (RRL: Spikman et al., 2010) is a semi-structured interview that measures patients' level of participation in different societal domains (i.e. work, social relations, leisure activities and mobility; max. score=16). At all time-points patients were asked to compare their current level of participation to their participation level before diagnosis. A higher score reflects a lower level of participation.

## *Other outcome measures*

### NEUROPSYCHOLOGICAL TEST MEASURES

#### Executive functions

EF were assessed with the Trail Making Test B/A ratio (TMT B/A: (Reitan, 1958)), the Visual Elevator subtest of the Test of Everyday Attention (TEA; number correct: (Robertson, Ward, & Ridgeway, V. & Nimmo-Smith, I., 1994)) and the Behavioural Assessment of the Dysexecutive Syndrome (BADS; age score: (Wilson, Alderman, Burgess, Emslie, & Evans, 1996)). Of the BADS subtests, the complex Zoo map subtest (total score) was also independently analysed.

#### Attention and memory functions

The Trail Making Test A (TMT A: Reitan, 1985) was used to measure selective attention and the RAVLT ((Deelman et al., 1980), a verbal memory test, measured immediate recall (IR) and delayed recall (DR).

### RATING OF GOAL ATTAINMENT

Treatment goal attainment (TGA; Spikman et al., 2010) was used to measure treatment effectiveness as experienced by the patients. During the third session of each treatment, patients had formulated three personal goals which were related to executive dysfunctions in everyday life. Pre- and post-treatment, patients rated their level of functioning on these goals on a ten point scale (10=max., per assessment the mean score of three goals was used). At both post-treatment assessments, patients rated their level of functioning again (TGA: per assessment the mean score of three goals).

### QUESTIONNAIRES

The Dysexecutive Questionnaire (DEX; total score: (Burgess et al., 1996) was used to assess problems in executive functioning in everyday life. The questionnaire was completed by participants (i.e. self-version) and patients' significant others (i.e. proxy version). Healthy controls completed only the self-version of the DEX. A higher score reflects more problems with executive functioning in everyday life.

The Brock Adaptive Functioning Questionnaire (BAFQ: (Dywan, 1996)) was used to measure aspects of adaptive functioning. Both a self and a proxy version were used. For the purpose of this study, only the scales related to EF were used (i.e. 'Planning', 'Initiative', 'Flexibility', 'Excess caution' and 'Impulsivity'). A mean total score of these subscales was calculated. A higher score represented more complaints.

In order to assess patients' health-related QoL, the Parkinson Disease Questionnaire (PDQ-39; total score (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997)) was used. A higher score indicated a lower level of QoL.

Caregiver burden was assessed with the short form of the Zarit Burden Interview (ZBI; total score: (Zarit, Orr, & Zarit, 1985)), which was completed by patients' significant others. A higher score was related to a higher caregiver burden.

## Statistical analyses

IBM Statistical Package for the Social Sciences version 22 was used for data analyses. Independent samples t-tests and non-parametric tests were used to compare descriptive and disease characteristics between patients with PD and controls and between treatment groups. Independent samples t-tests were also used to compare performances on neuropsychological tests of (1) patients with PD in the experimental condition and patients in the control condition at T0 and (2) patients with PD and healthy controls at T0. Treatment effects were analysed with repeated measures ANOVAs. This univariate analysis was chosen in order to minimise data loss due to missing values. The dependent variables were the RRL, TGA, DEX-self, DEX-proxy, BAFQ EF-self, BAFQ EF-proxy, TMT B/A, BADS age score, TEA visual elevator, TMT A, PDQ-39 and ZBI. Possible time and interaction effects of the treatment conditions with respect to these outcome measures were analysed in two steps: T1 versus T0 and T2 versus T0. In addition, the effect sizes (partial-eta-squared) were calculated. An effect size of 0.01 was labelled as small, 0.06 as medium and 0.14 as large (Fritz, Morris, & Richler, 2012). For statistical analyses an alpha of 0.05 was applied. At T2 the percentage of missing values was 15.4% for the primary outcome measure (RRL), 17.9% for the ZBI, 15.4% for the TEA map search, 10.3% for the BAFQ proxy version and 2.6% at maximum for the other outcome measures. This was mainly due to logistic reasons within one of the participating centres.

# Results

## Comparisons at baseline

Table 2 shows that Patients with PD reported significantly more problems at baseline (T0) with executive functioning in everyday life than healthy controls. Furthermore, it was found that PD patients' performance was significantly lower on objective tests of EF and attention compared to healthy controls.

Tables 1 and 3 show that there were no significant differences at T0 between the experimental (ReSET) and control (Cogniplus) group with regard to descriptive and disease characteristics, global level of cognitive functioning (SCOPA-COG), symptoms of anxiety and depression and any of the outcome measures.

**Table 3. Baseline performance of patients with PD in both treatment conditions on primary and secondary outcome measures.**

| | ReSET (n=24) | Cogniplus (n=19) | | |
|---|---|---|---|---|
| | M (SD) | M (SD) | t | *p* |
| **Primary outcome** | | | | |
| RRL total | 4.77 (2.00) | 4.67 (2.72) | 0.14 | 0.888 |
| **Neuropsychological tests** | | | | |
| EF | | | | |
| TMT B/A | 2.52 (1.05) | 2.65 (0.86) | -0.43 | 0.672 |
| Zoo-map total score | 7.88 (5.62) | 5.79 (6.28) | 1.15 | 0.258 |
| BADS age score | 97.17 (15.73) | 99.63 (9.56) | -0.60 | 0.552 |
| TEA visual elevator | 7.14 (2.21) | 7.87 (2.70) | -0.90 | 0.373 |
| Attention & memory | | | | |
| TMT A | 46.38 (13.25) | 40.37 (14.07) | 1.44 | 0.158 |
| RAVLT IR | 38.08 (11.59) | 37.42 (10.53) | 0.19 | 0.847 |
| RAVLT DR | 7.50 (3.34) | 8.32 (2.98) | -0.83 | 0.409 |
| **Questionnaires** | | | | |
| EF | | | | |
| TGA | 4.50 (1.04) | 4.23 (1.37) | 0.74 | 0.465 |
| DEX self | 24.08 (10.66) | 24.79 (10.89) | -1.17 | 0.252 |
| DEX proxy | 20.74 (14.75) | 22.26 (10.98) | -1.80 | 0.087 |
| BAFQ-EF self | 2.27 (0.55) | 2.40 (0.48) | -0.79 | 0.437 |
| BAFQ-EF proxy | 2.11 (0.71) | 2.36 (0.59) | -1.14 | 0.264 |
| QoL & caregiver burden | | | | |
| PDQ-39 | 44.50 (21.43) | 52.74 (21.28) | -1.26 | 0.216 |
| ZBI | 10.32 (7.68) | 10.21 (9.57) | 0.04 | 0.968 |

*Note.* RRL = Role Resumption List; TMT B/A = Trail Making Test B/A ratio; BADS age score = Behavioural Assessment of the Dysexecutive Syndrome total standard age score; TEA = Test of Everyday Attention; TMT A = Trail Making Test A; RAVLT IR = Rey Auditory Verbal Learning Test immediate recall; DR = delayed recall; TGA = Treatment goal attainment; DEX = Dysexecutive Questionnaire; BAFQ-EF = Brock Adaptive Functioning Questionnaire: sum of executive function scales; PDQ-39 = Parkinson's Disease Questionnaire; ZBI = Zarit Burden Interview.

## Effects of treatment

Table 4 shows the results of the repeated measures analyses of T1 versus T0. No difference was found between T0 and T1 or between groups on the primary outcome measure (RRL). Also, small effect sizes were found for these comparisons. Patients in both treatment conditions reported a significant improvement of functioning related to their treatment goals (TGA) at T1, with patients in the ReSET condition showing a significantly greater improvement than patients in the Cogniplus condition (large to medium effect sizes respectively). Furthermore, at T1 both treatment groups showed a significant reduction of problems on the DEX-self compared with T0, with patients in the ReSET condition showing a significantly larger reduction than patients in the control condition (medium effect size). In both groups at T1, patients' significant others did not report a reduction of problems on the DEX-proxy compared with T0. No differences were found regarding the performances on the neuropsychological tests, BAFQ-self and proxy version, PDQ-39 and Zarit.

Table 5 shows the results of the repeated measures analyses of T2 versus T0. No difference was found between T0 and T2 and between groups on the RRL (medium and small effect sizes, respectively). Furthermore, patients in both treatment conditions still reported a significant improvement at T2 of TGA compared with T0 (large effect sizes). However, there is no difference between the groups (medium effect size). At T2 the number of problems reported on the DEX-self in both treatment groups was also significantly reduced compared with T0, but there was no significant difference between the groups (large to small effect sizes, respectively). In both groups, patients' significant others did not report a reduction of the problems on the DEX-proxy at T2 compared with T0 (medium effect size). Regarding the performances on neuropsychological tests, only a significant interaction was found for the Visual elevator. For both treatment groups no time or interaction effects were found on the BAFQ-self and proxy version, PDQ-39 and Zarit at T2.

**Table 4. Results of repeated measures analyses comparing performances on all outcome measures between T1 and T0 for the experimental and control groups.**

| | ReSET (n=24) | | Cogniplus (n=19) | | ANOVA RM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time | | | Time x group | | |
| | M T0 (SD) | M T1 (SD) | M T0 (SD) | M T1 (SD) | F | p | $n^2_p$ | F | *p* | $n^2_p$ |
| **Primary outcome** | | | | | | | | | | |
| RRL total | 4.77 (2.00) | 5.05 (2.28) | 4.94 (2.77) | 4.81 (2.81) | 0.15 | 0.700 | 0.00 | 1.10 | 0.302 | 0.03 |
| **Neuropsychological tests** | | | | | | | | | | |
| EF | | | | | | | | | | |
| TMT B/A | 2.52 (1.05) | 2.49 (1.05) | 2.51 (0.66) | 2.57 (1.04) | 0.02 | 0.904 | 0.00 | 0.08 | 0.774 | 0.00 |
| BADS age score | 96.43 (15.66) | 99.63 (9.56) | 99.35 (14.60) | 98.84 (20.21) | 0.20 | 0.657 | 0.00 | 0.61 | 0.440 | 0.02 |
| TEA visual elevator | 7.14 (2.21) | 7.86 (2.01) | 7.93 (2.79) | 7.43 (2.41) | 0.09 | 0.764 | 0.00 | 2.67 | 0.111 | 0.07 |
| Attention | | | | | | | | | | |
| TMT A | 46.38 (13.25) | 39.56 (14.01) | 46.42 (18.69) | 42.44 (22.36) | 0.53 | 0.470 | 0.01 | 0.50 | 0.482 | 0.01 |
| **Rating of goals** | | | | | | | | | | |
| TGA | 4.50 (1.04) | 6.10 (1.14) | 4.23 (1.37) | 4.88 (1.15) | 29.88 | <0.001** | 0.42 | 5.32 | 0.026* | 0.12 |
| **Questionnaires** | | | | | | | | | | |
| EF | | | | | | | | | | |
| DEX self | 24.08 (10.66) | 18.79 (9.81) | 23.67 (10.01) | 23.39 (12.07) | 5.13 | 0.029* | 0.11 | 4.16 | 0.048* | 0.09 |
| DEX proxy | 20.74 (14.75) | 19.78 (13.59) | 21.18 (11.01) | 19.65 (11.51) | 0.77 | 0.386 | 0.02 | 0.04 | 0.841 | 0.01 |
| BAFQ-EF self | 2.27 (0.55) | 2.78 (0.48) | 2.40 (0.48) | 2.41 (0.52) | 0.01 | 0.941 | 0.00 | 0.00 | 0.969 | 0.00 |
| BAFQ-EF proxy | 2.11 (0.71) | 2.17 (0.64) | 2.38 (0.60) | 2.46 (0.53) | 1.51 | 0.226 | 0.04 | 0.06 | 0.808 | 0.00 |
| QoL & caregiver burden | | | | | | | | | | |
| PDQ-39 | 44.50 (21.43) | 43.71 (19.78) | 50.28 (18.92) | 52.06 (24.16) | 0.08 | 0.773 | 0.00 | 0.57 | 0.454 | 0.01 |
| ZBI | 10.65 (7.83) | 9.80 (9.04) | 9.79 (9.08) | 11.00 (7.54) | 0.03 | 0.866 | 0.00 | 0.93 | 0.342 | 0.03 |

*Note.* RRL = Role Resumption List; TMT B/A = Trail Making Test B/A ratio; BADS age score = Behavioural Assessment of the Dysexecutive Syndrome total standard age score; TEA = Test of Everyday Attention; TMT A = Trail Making Test A; TGA = Treatment goal attainment; DEX = Dysexecutive Questionnaire; BAFQ-EF = Brock Adaptive Functioning Questionnaire: sum of executive function scales; PDQ-39 = Parkinson's Disease Questionnaire; ZBI = Zarit Burden Interview.

**Table 5. Results of repeated measures analyses comparing performances on all outcome measures between T2 and T0 for the experimental and control groups.**

| | ReSET (n=22) | | Cogniplus (n=17) | | ANOVA RM | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Time | | | Time x group | | |
| | M T0 (SD) | M T2 (SD) | M T0 (SD) | M T2 (SD) | F | *p* | $n^2_p$ | F | *p* | $n^2_p$ |
| **Primary outcome** | | | | | | | | | | |
| RRL total | 5.11 (1.94) | 5.74 (2.00) | 5.08 (2.96) | 5.38 (2.33) | 3.84 | 0.059 | 0.11 | 0.46 | 0.504 | 0.02 |
| **Neuropsychological tests** | | | | | | | | | | |
| EF | | | | | | | | | | |
| TMT B/A | 2.49 (1.06) | 2.65 (0.82) | 2.50 (0.68) | 2.60 (0.99) | 0.64 | 0.427 | 0.02 | 0.04 | 0.836 | 0.00 |
| BADS age score | 98.00 (13.49) | 98.05 (18.85) | 100.50 (8.66) | 106.94 (12.61) | 1.43 | 0.239 | 0.04 | 1.39 | 0.245 | 0.04 |
| TEA visual elevator | 7.32 (2.00) | 7.89 (1.94) | 8.15 (2.51) | 6.77 (2.62) | 1.28 | 0.267 | 0.04 | 7.59 | 0.010* | 0.20 |
| Attention | | | | | | | | | | |
| TMT A | 45.00 (11.33) | 38.47 (13.64) | 41.09 (14.14) | 40.53 (23.35) | 0.23 | 0.634 | 0.06 | 2.40 | 0.130 | 0.06 |
| **Rating of goals** | | | | | | | | | | |
| TGA | 4.48 (1.09) | 5.88 (1.05) | 4.33 (1.41) | 5.10 (1.36) | 28.89 | <0.001** | 0.45 | 2.40 | 0.130 | 0.06 |
| **Questionnaires** | | | | | | | | | | |
| EF | | | | | | | | | | |
| DEX self | 24.82 (10.49) | 20.59 (10.47) | 24.50 (11.00) | 21.00 (9.11) | 8.73 | 0.005* | 0.20 | 0.08 | 0.782 | 0.00 |
| DEX proxy | 20.36 (14.99) | 17.91 (13.99) | 20.86 (11.61) | 23.36 (11.63) | 0.00 | 0.986 | 0.00 | 3.95 | 0.055 | 0.10 |
| BAFQ-EF self | 2.29 (0.57) | 2.21 (0.53) | 2.35 (0.48) | 2.30 (0.38) | 1.32 | 0.258 | 0.04 | 0.08 | 0.778 | 0.00 |
| BAFQ-EF proxy | 2.13 (0.73) | 2.14 (0.65) | 2.23 (0.55) | 2.24 (0.57) | 0.01 | 0.908 | 0.00 | 0.00 | 0.964 | 0.00 |
| QoI & caregiver burden | | | | | | | | | | |
| PDQ-39 | 45.23 (21.89) | 43.59 (23.73) | 52.38 (23.23) | 49.88 (20.57) | 0.99 | 0.327 | 0.03 | 0.04 | 0.837 | 0.00 |
| ZBI | 10.89 (8.02) | 10.33 (8.46) | 8.92 (9.72) | 9.62 (7.86) | 0.00 | 0.959 | 0.00 | 0.23 | 0.637 | 0.01 |

*Note.* RRL = Role Resumption List; TMT B/A = Trail Making Test B/A ratio; BADS age score = Behavioural Assessment of the Dysexecutive Syndrome total standard age score; TEA = Test of Everyday Attention; TMT A = Trailmaking Test A; DEX = Dysexecutive Questionnaire; BAFQ-EF = Brock Adaptive Functioning Questionnaire: sum of executive function scales; PDQ-39 = Parkinson's Disease Questionnaire; ZBI = Zarit Burden Interview.

# Discussion

This is the first RCT that studied the effectiveness of a strategy training (ReSET) for improving EF in everyday life, level of participation and QoL in patients with PD. Recent studies concluded that cognitive training is feasible and beneficial for patients with PD with EF deficits. However, these studies evaluated protocols that were primarily based on cognitive training (i.e. repetitive practise of (computerised) tasks in order to strengthen EF) but restricted their measurement of treatment outcome to performances on neuropsychological tests. Hence, it remained unclear whether there was an effect of treatment on everyday life executive functioning of patients with PD and whether this lasted over time. Foster et al. (2017) recently showed that also strategy training is feasible for patients with PD; however, the effectiveness of their intervention was not investigated. The primary aim of the current study was to investigate whether a strategy training for EF, called Reset, would improve PD patients' functioning in everyday life more than a cognitive training (Cogniplus) and whether this effect would last over time.

Unfortunately, ReSET did not lead to overall improvement on measures of everyday life executive functioning in the long term. However, immediately after treatment patients in the strategy training group (ReSET) reported to have attained their goals to a larger extent and to have experienced fewer executive complaints than patients in the control condition receiving cognitive computerised training (Cogniplus). At follow up this group difference had disappeared although both patient groups still reported improvement compared to pre-treatment functioning on both, relatively subjective measures (i.e. goals and DEX questionnaire). We found no changes on other measures of everyday life executive functioning or on neuropsychological tests for EF for both treatment groups after treatment. The drop-out rate during treatment was relatively small (n=6), showing that the majority of patients with PD with a relatively mild disease severity (H&Y I-III) were able to complete the treatment programmes in an outpatient setting. This underlines the finding of Foster et al. (2017) that, as with cognitive training, also cognitive rehabilitation programmes based on strategy training can be feasible for patients with PD

We did not find significant effects of ReSET and Cogniplus on the primary outcome measure, the RRL. This measure was chosen because it had been proved to be a valid measure of the effectiveness of EF strategy training on participation level of ABI patients in a previous study (Spikman et al., 2010). In the present study, however, patients with PD showed no improvement with regard to their level of participation (work, social relations, leisure and mobility) irrespective of the type of treatment they received. There are several explanations for this lack of result. First, the RRL assesses

participation by requiring patients to compare their current participation level to a previous level in the period prior to the diagnosis of PD. In contrast to patients with ABI, for patients with PD the moment of onset of the disease is not always clear cut since the majority of patients were diagnosed after a long period (sometimes years) of having gradually progressing symptoms. Furthermore, for many patients reporting a decreased participation with regard to work, social activities, leisure or mobility this was not always clearly related to cognitive dysfunction; patients indicated that motor impairments and fatigue had a significant negative influence as well. In addition, the majority of patients were already unemployed pre-treatment, either because they had already reached their retirement age (the patients with PD were on average older than the ABI group in the study of Spikman et al., 2010) or because they had quit their job before retirement age because of Parkinson related symptoms. For these patients, functioning on the work-subscale of the RRL could not be rated, narrowing the score range substantially. For these reasons, we deem the RRL far less suitable and less sensitive to measure changes in participation in patients with PD than had been the case for ABI patients.

At baseline, the patients with PD showed impairments on all neuropsychological tests for EF and attention, when compared to healthy controls. Patients with PD also reported significantly more problems with executive functioning in everyday life (DEX) than healthy controls. Furthermore, at baseline the ReSET and Cogniplus group did not differ with regard to demographic and disease characteristics, performance on objective neuropsychological tests and the number of problems with EF in everyday life, level of participation and QoL. Thus, prior to treatment both treatment groups did not differ from each other, which indicates that differences between groups found after treatment cannot be explained by differences between the groups at baseline.

The finding that patients in both treatment groups reported some improvement on two subjective indications of executive functioning, with a slight advantage for the ReSET group directly after treatment but that disappeared at follow up, strongly suggests that patients subjectively experienced some benefit of treatment. However, for both groups the significant others of the patients with PD did not report to have observed a reduction of the EF problems that patients exhibit in everyday life. This contrast suggests that the reduction of problems that patients experience is not visible to others and may indicate merely that patients have attained a higher level of control and self-efficacy, i.e. that they have gained more confidence in their ability to plan and execute everyday life tasks, regardless of whether this is actually the case. Since previous studies have demonstrated that perceived self-control and self-efficacy matter when it comes to dealing with a chronic illness such as PD in relation to well-being, we deem this a relevant finding (Kuijer & De Ridder, 2003; Rosqvist et al., 2016; Thombs, Kwakkenbos, Riehm, Saadat, & Fedoruk, 2017).

Nevertheless, we could not demonstrate that ReSET or Cogniplus resulted in significant improvement of PD patients' QoL or in a decrease of their caregivers' burden. Given that PD patients' functioning will gradually deteriorate over time because of the neurodegenerative character, one could also argue that finding no change in QoL and caregivers' burden over time is in fact a positive outcome. An additional explanation for lack of change regarding caregiver burden may be that the average caregivers' reported burden before treatment was already rather low (M=8.92-11.00; max. 48), which reduces the possibility to find improvement on this measure.

With regard to neuropsychological tests for EF, a significant interaction effect was found at 3-5 months post-treatment on the TEA Visual elevator test. Contrary to our expectation, patients who received ReSET showed a slightly better performance than at baseline, whereas the performance of the control group had worsened. This finding is hard to explain, because if improvement on such a task was expected this would be the case for those patients who received the attention training in the Cogniplus protocol. Furthermore, for both treatment groups we did not find improved performance after treatment on the other neuropsychological tests for EF and attention. Previous studies that examined cognitive training in PD sometimes showed improvement on neuropsychological tests (Calleo et al., 2012; Leung et al., 2015). However, it has been demonstrated that cognitive training that primarily aims at improving specific cognitive functions only leads to improvement on neuropsychological measures that bear great resemblance to the tasks that were used in the treatment (near-effects), whereas only rarely has improvement been found on other neuropsychological tests or on measures for everyday life functioning (far-effects) (Cicerone et al., 2011). However, the primary aim of ReSET in this study was to teach patients compensatory strategies in order to better cope with their impairments in EF in everyday life. Hence, we expected not to find changes on neuropsychological tests for EF. Even more so, these tests are considered to be less sensitive to changes in functioning because they have to be complex and new to require the use of EF, which will not be the case when used for repeated assessment.

The current study has some limitations that need to be mentioned. First, only patients with a mild to moderate disease severity (H&Y stage 1 to 3) were included. However, in more severely impaired patients (H&Y stage 4 and 5) it is very likely that cognitive impairments will become more frequent and more severe, and that the percentage of patients who develop dementia will increase. We expect that cognitive rehabilitation aimed to learn and apply a strategy will be too demanding for the cognitive capacities of this subgroup. Possibly, these patients can still benefit from skill training (i.e. training of specific activities), which offers more structure. This is an interesting topic for future studies. In general, the sample size was small, which had a negative influence on the power. However, compared to previous studies on

neuropsychological rehabilitation in patients with PD, the sample sizes are relatively large. Another limitation is that at T2 the percentage of missing values was unfortunately high for some outcome measures. Consequently, it might be that significant results were not found due to a lack of power. Furthermore, another limitation pertaining to the amount of time spent on training was not equal for both conditions. Even though both ReSET and Cogniplus consisted of 14 one-hour sessions, patients in the ReSET group had to spend additional time because practising the planning and execution of everyday activities in their home environment was an important element of the strategy training, whereas patients in the Cogniplus group could only practise during the session itself.

In conclusion, this study demonstrates that patients with PD with a mild disease severity (H&Y ≤ 3) were able to adhere to a neuropsychological rehabilitation programme, despite of their motor symptoms and fatigue, as indicated by the low drop-out rate. This indicates that participating in the treatment programmes ReSET, and Cogniplus, is feasible for this group of patients with PD. With regard to the effectiveness of both treatment programmes, the results of the present study show that both cognitive rehabilitation including strategy training (ReSET) and cognitive training (Cogniplus) lead to some self-reported subjective improvement of executive functioning in everyday life, with a slight advantage of ReSET directly after treatment compared to the Cogniplus. This suggests that patients subjectively experienced some benefit of neuropsychological rehabilitation in general (i.e. may seem to have attained a higher level of control and self-efficacy regarding executive functioning in everyday life), even though this was not visible to their significant others.

Because of the neurodegenerative character of PD, future research should focus on determining up to which point in the progression of the disease patients are actually able to learn and benefit from cognitive rehabilitation programmes based on strategy training. A large number of patients will eventually develop a dementia (Vasconcellos & Pereira, 2015), which means that providing external structure will become more and more important when the disease progresses. Therefore, we deem it worthwhile to involve caregivers more intensively during treatment sessions, so they can gradually increase their assistance in structuring patients' everyday life activities over time. Furthermore, because of the heterogeneity and complexity of the disease, it is highly important to tailor treatment programmes to patients' individual needs for use in clinical practice. Finally, because of the progressive character of PD, which leads to deterioration of patients' physical and cognitive functioning in everyday life, not only improvement of PD patient' level of everyday life functioning should be considered a desirable outcome of neuropsychological rehabilitation, but also a stabilization of their level of functioning for a longer time period than would be the case for patients who do not receive treatment would be advantageous.

## Geolocation information

This study was conducted in three medical centres in the Netherlands: 1) the University Medical Centre Groningen located in Groningen, the Netherlands; 2) Nij Smellinghe a medical centre located in Drachten, the Netherlands; and 3) Maastricht University Medical Centre located in Maastricht, the Netherlands.

## Acknowledgements

This work was supported by the Dutch Organization for Scientific Research (NWO), the National Initiative Brain and Cognition (NIHC) under Grant (056-11-012). This quick-result project is embedded in the pillar 'The Healthy Brain, Program Cognitive Rehabilitation'.

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**Chapter 7**

# Summary and general discussion

# Summary

In **chapter one** a general introduction is given on Parkinson's disease, executive functions (EF) and neuropsychological assessment of EF. Furthermore, the principles of neuropsychological rehabilitation and cognitive training are illustrated. The general introduction closes with the thesis aim and outline. The aim of this thesis was to characterize EF related to its assessment and to evaluate a strategic training in patients with PD.

The primary aim of our study as described in **chapter two,** was to determine whether patients with PD show mental slowness (bradyphrenia) apart from the assumed motor slowness (bradykinesia). In this study the use of the term bradykinesia primarily refers to the aspect of motor slowness. Patients with PD were assumed to show motor slowness and to a certain extent mental slowness in comparison with healthy controls. In addition the study hypothesised that particularly mental slowness, if found, would have a negative influence on patients´ neuropsychological test performance. This was investigated with a simple reaction time task (Vienna Test System) that offered the possibility to distinguish between a mental component (i.e. reaction time) and a motor component of the response (i.e. motor time). Surprisingly, no significant differences were found when the motor times of patients with PD were compared to the motor times of healthy controls. Patients with PD showed however significantly slower reaction times than healthy controls. We therefore concluded that patients with PD show mental slowness apart from motor slowness. Reaction and motor times of patients with PD were not related to clinical measures of disease severity (i.e. H&Y and UPDRS-III). Mental speed was not a predictor of neuropsychological test performance, however motor times were a significant predictor of performance on two tests of attention (TMT A and Stroop Color-Word/Color card ratio). This finding implicates that for patients with PD motor slowness needs to be taken into account when interpreting results on these tests.

In **chapter three** we investigated whether objective measures (i.e. neuropsychological tests) and subjective measures (i.e. questionnaires) of EF are associated in a group of non-demented patients with PD. Furthermore, it was investigated whether impairments in EF measured with tests predict patients' level of participation and QoL. No associations were found between objective and subjective measures of EF, indicating that each set of measures represents a unique part of the spectrum of EF problems of these patients. Both types of measures, gender and disease severity were moderate predictors of participation and/or QoL in patients with PD.

In **chapter four** we compared the general cognitive and executive profile (based on neuropsychological test performance) and needs and aims (as

operationalised by individual treatment goals) of patients with PD to a group of ABI patients to investigate whether there are structural differences between both groups that might justify why cognitive rehabilitation is not yet offered as standard therapy in patients with PD. Patients underwent an extensive neuropsychological test battery and set three individual goals they wanted to attain by means of the EF treatment. These goals were first classified into domains of EF and subsequently into domains of basic functioning, daily life activities and participation. We found that PD and ABI patients' neuropsychological profile as well as their goals were highly comparable. Interestingly, patients with PD set more goals related to "time management" (aspect of EF) and "housekeeping and gardening" (domains of everyday life functioning) than ABI patients. In sum, we found no reasons to assume that patients with PD cannot benefit from strategic executive training.

**Chapter five** presents a review on cognitive rehabilitation in patients with PD. Knowing that impairments in EF are predominant in PD, specific attention was given to the extent to which the included studies focused on improving impairments in EF. Nine studies (2004-2013) were included and evaluated in terms of methodological quality and effectiveness. In addition, these rehabilitation programmes were classified regarding type of training applied (i.e. function, skill and strategy training) and the outcome measures were classified into three ICF levels: function level, activity/participation level and psychosocial level. Findings of these studies indicate that cognitive rehabilitation is feasible and effective in terms of improving cognitive functioning measured with neuropsychological tests. An important limitation of these studies is that the majority of treatment programmes included function training only and also measured outcome on function level only. Thus, it remains unclear whether effects generalize to everyday life functioning for patients with PD. Besides, relatively little attention was paid to treatment of impairments in EF. Since strategy training was found to be effective for ABI patients, we conclude that future research is needed to study the effectiveness of strategy training in improving executive functioning in everyday life, participation in societal domains and QoL in patients with PD.

**Chapter six** describes the results of the RCT we carried out on the effectiveness of ReSET; a Strategic Executive Treatment compared to a computerised function training (Cogniplus) in patients with PD. At 2 weeks and 3-5 months post-treatment, patients in both the ReSET and Cogniplus condition reported an improvement in functioning regarding their individual treatment goals and reported a decreased number of executive complaints in everyday life functioning. Only at two weeks post-treatment this self-reported improvement was significantly greater in the ReSET group than in the Cogniplus group. Patients' significant others in both groups did, however, not report a significant decrease of executive problems after treatment. Therefore, we suggested that it was mainly patients' belief of self-efficacy that might have been strengthened after treatment, which was apparently not observable for

significant others in terms of improved functioning in everyday life activities. Both treatments had no effect on patients' general level of participation and QoL. This means that we found insufficient evidence to confirm the hypothesis that, as it was found in ABI patients (Spikman et al., 2010), strategy training is more effective than function training for improving impairments in EF in everyday life functioning, level of participation and QoL in patients with PD. Future research should focus on investigating for which specific group of patients with PD which type of treatment is most beneficial in terms of improving everyday life functioning and QoL.

**Chapter 7** comprises a general discussion of the preceding chapters, in which the most important results are summarized and in particular the clinical relevance of these conclusions is described. Furthermore, recommendations for future research are made based on the clinical lessons that have been learned from the studies as described in the individual chapters.

# General discussion

In this section we will discuss the main issues related to both the assessment and treatment of impairments in EF in patients with PD, based on the studies that were summarized in the previous section.

## Slowness in PD: mental versus motor slowness

Bradykinesia (i.e. slowness and diminished amplitude of movement) is one of the core motor symptoms in PD. In addition, bradyphrenia or slowness of information processing is believed to be common in patients with PD as well. A long-standing research question we tried to answer in this thesis was whether patients with PD show mental slowness in addition to motor slowness, or in other words whether mental and motor slowness can be distinguished. If so, a subsequent question pertains to which type of slowness is dominant in terms of affecting performance on neuropsychological tests of attention, memory and EF.

In our study as described in chapter 2, we used a reaction time task (Vienna Test System) to differentiate between a mental speed of information processing component (i.e. reaction time= time between presentation of stimulus to lifting the index finger from the rest key) and a motor component (i.e. motor time = time between lifting the finger from rest key to response key) of the response. We found that patients with PD showed slower reaction times than healthy controls, but contrary to our expectations, their average motor times were not slower than those of healthy controls. An important remark here is that all patients were on dopamine medication while tested, which may have interfered with a valid measurement of motor slowness. Furthermore, we had expected to find an association between the

(on medication) UPDRS-III score and the degree of motor slowness in patients with PD. However, no significant correlation was found. A possible explanation for this finding could be that in addition to bradykinesia, the UPDRS-III measures a range of other motor symptoms (e.g. rigidity and postural balance) and as such lacks specificity. To overcome this problem the sum score of the relevant UPDRS-III items should be used to operationalize bradykinesia. Unfortunately, in most patients´ medical files of our samples only a total score on the UPDRS-III was reported.

Another interesting explanation refers to the assumption that slow motor times reflect bradykinesia and whether this is correct. Given the recent literature (Wu et al., 2015), bradykinesia and other motor symptoms of PD are thought to be the result of an underlying impaired motor automaticity instead of basic slowness of the actual executed movement itself. Because of degeneration of dopamine producing neurons in the basal ganglia, especially the function of the sensorimotor striatum becomes impaired, which is essential in facilitating automatic motor behaviour in healthy people. As a consequence, a higher degree of attentional control provided by cortical regions and specifically the associate striatum is needed in order to consciously initiate motor behaviour. This indirect route is per definition slower than when motor behaviour is generated automatically, since each sub-movement has to be initiated in an effortful, conscious manner. Wu et al. (2015) describe that even simple repetitive movements as measured with the UPDRS-III (e.g. finger tapping) are automatically executed by healthy people, whereas patients with PD have difficulty with internally generating these movements. This suggests that the clinically observed slowness of movement, defined as bradykinesia, might be interpreted as apathy-driven slowness. This means that very likely it is caused by an accumulation of repeatedly delayed initiation of movements instead of a slow execution of the movements itself. This might explain the lack of correlation between motor times and the UPDRS-III total score, since the motor times in the reaction task refer to the pure motor action, filtering out the initiation of the movement.

Following this line of arguments, it is plausible that if the slowness in the reaction time task is related to an initiation problem, this will likely affect the execution of everyday life activities in patients with PD, in which we observed difficulties during the ReSET programme. The execution and completion of everyday life activities (e.g. cooking) requires the initiation of a series of sub-actions which needs to be internally generated. In healthy people daily behavioural routines like brushing your teeth or eating breakfast with a spoon are carried out automatically (Wu et al., 2015). For patients with PD, because of their automatization problems, more attentional control will be required to initiate these sub-actions resulting into a delay of the execution of the specific behavioural routine. This is in line with the clinical experience that patients with PD especially have difficulty with estimating the time necessary to execute their plans (which they are able to make) and with initiating

the execution of a task, while they do know how to do it. In terms of Ylvisaker's (1998) classification of aspects of EF, we postulate that apathy-driven 'initiation' seems to be the aspect that is primarily affected and thus can be considered a core impairment in EF in patients with PD.

## Cognitive rehabilitation: what is the merit?

The question whether patients in PD would benefit from strategy training was a major topic in this thesis. Based on the results we can conclude that at two weeks and 3-5 months post-treatment, patients in both the ReSET and Cogniplus condition reported an improvement in functioning on their individual goals and reported a decreased number of executive complaints in everyday life functioning (DEX). Two weeks post-treatment, this self-reported improvement was significantly greater in the ReSET group than in the Cogniplus group. Although this improvement was not reported by patients' relatives, we believe that this may be an important and promising finding with respect to outcome on a participation level. We could interpret the results as an increase in the extent to which patients' perceived to have control in daily life situations that is related to self-efficacy. Self-efficacy in turn has been found to positively affect overall well-being and QoL (Bowen et al., 2015). However, in our study no effects were found for both treatments on the level of participation and QoL. As such, our study did not support a superior effect of strategic training over functional training, as was described in ABI patients (Spikman, Boelen, Lamberts, Brouwer, & Fasotti, 2010).

One explanation for this lack of finding is that although ABI and patients with PD may have EF impairments in common, there are still differences in terms of disease related demographic characteristics and symptomatology. For instance, PD is a neurodegenerative disease characterised by a progressive course that leads to gradual deterioration of (motor) functioning, independency and level of participation, whether the cause of ABI is usually readily apparent with symptoms becoming manifest shortly after the injury (more acute type of brain injury). Also, patients with ABI and PD are confronted with their impairments in different stages of their lives, with ABI patients having a younger mean age at onset than Parkinson's disease (usually onset between 50-60 years). This means that impairments in EF influence the level of participation (i.e. work, social relations, leisure activities and mobility) for patients with ABI and PD in a different way and to a different extent. For example, a majority of the patients with PD was unemployed because they either reached the age of retirement or were found to be unable to work because of motor impairments. Resumption of work was not a realistic nor desired goal for those patients. Except for possible cognitive and executive impairments, participation in the domains of social relations, leisure activities and mobility was also frequently limited in patients with PD

due to their motor impairments (e.g. bradykinesia, tremor, postural instability) and fatigue. For instance patients were less involved in social and leisure activities because they felt too tired and became unable to drive a car, which limited their mobility. Daily activities in patients with PD are usually much more confined to activities that can be done in and around the house than those for ABI patients. Also, when PD progresses, mobility of patients decreases further and they become even more home bound. The relatively young ABI group in the study of Spikman et al. (2010) was actively participating in the mentioned domains until they were suddenly unable to participate due to the acute type of brain injury (e.g. unable to work, unable to keep up their social relations). Results showed that strategic executive training helped these patients to actually resume those societal roles.

We conclude that for patients with PD it is more important and realistic to focus on stabilization rather than improvement of their level of participation in terms of increasing activities in societal domains instead of resumption of previous roles. Stabilization of the participation level and QoL as long as possible should be considered as a beneficial outcome.

Another explanation for the lack of treatment effects on the participation and QoL in patients with PD might be related to the specific clinical characteristics of our sample as experienced during treatment. The General Planning Approach has a central role within the strategic executive treatment (ReSET). This approach helps patients to execute everyday life activities more efficiently by teaching them to consciously formulate the goal of the activity, determine the individual steps that need to be carried out, put the steps in the right order and describe the materials and expected time that will be needed per step. When using this approach, patients are provided with a structure which helps them to actually execute and complete the intended activity and as such may provide feelings of control. The previous study of Spikman et al. (2010) proved that this approach was beneficial for ABI patients, since these patients had especially problems to come up with the individual steps and to execute these steps in a logical order. For the majority of patients with PD, however, we found that formulating the individual steps for a certain activity and putting them in the right order was not a major problem. Therefore, the merit of using GPA was mainly to obtain a realistic view of the actual time needed for activities and sub-steps. It appeared that patients with PD estimated the needed time mostly shorter than the actual time investment that was needed. In everyday life, patients with PD seemed to insufficiently take into account their apathy driven slowness when planning an activity, since they persisted in making the same daily to-do-lists as they were used to before their diagnosis. This frequently led to frustrations, because they could not complete their daily tasks in the estimated time span. Teaching how to use a diary efficiently was therefore another beneficial part of the ReSET protocol. Patients learned to routinely use a diary not only for important appointments, but even more

for planning everyday life activities in and around the house. This helped patients to obtain a visual overview of their week programme and to evaluate whether this was a realistic planning. Besides, the diary functioned as an external reminder for actually initiating activities and getting them done.

Our clinical experiences that impairments in EF in PD especially involve problems with time management are in line with the findings of the study described in chapter 5. When treatment goals of PD and ABI patients were classified into domains of EF, it appeared that patients with PD set significantly more goals related to time management than ABI patients. Thus, it seems that patients with PD are unable to adjust their daily schedule to their overall slowed tempo, which they experience as burdensome.

In sum, similarities but also some essential differences were found between the PD group described in this thesis and the group of ABI patients described in the previous study (Spikman et al., 2010), with regard to the presentation of impairments in EF and the extent and way these impairments hinder patients in their everyday life functioning. We conclude that in contrast to ABI patients, for patients with PD neuropsychological rehabilitation should not be aimed on resumption of roles or improvement of executive functioning. Instead the focus should be on maintaining their current level of everyday life functioning as long as possible, by providing them with tools to execute preferred activities in time.

## Clinical implications with regard to cognitive treatment of EF in patients with PD

One can question whether strategy training is the most preferred type of cognitive treatment in this group of patients with PD given our hypothesis that initiation problems play a central role in patients with PD. After all, the General Planning Approach and Goal Management Training still appeal strongly to patients' abilities to initiate and structure activities when applying these methods in everyday life. We suggest that skills training would possibly be a better alternative in patients with PD that encounter significant initiation problems. This type of training aims at improving the execution of specific everyday life activities by repetitive training of the sub-actions that are needed to accomplish the activity. In other words, training specific routines in order to re-automatize these routines without the purpose that these will generalize to other activities. Compared to strategy training, skills training offers more structure and depends less on patients' initiative. Moreover, the trainer is actively present when training patients and thus has the possibility to correct errors immediately. Errorless learning has a positive influence on the outcome but was not possible during our programme because of practical reasons. The execution of plans by making use of GPA and GMT could only be verbally evaluated in the following

session. For clinical practice, it can be valuable to collaborate with occupational therapists who do have the opportunity to train patients in their home environment.

Improving patients' feeling of self-efficacy can also be a valuable aim of treatment in itself, since a sense of self-efficacy is crucial for well-being and QoL (Bowen et al., 2015). Based on the findings of this thesis, computerised function training (Cogniplus) is also a good option for this purpose. Starting with such a function training gives patients the idea that they are actively working on reducing their problems. This may increase their sense of self-efficacy in the first place and might also motivate patients for further treatment.

## Is ReSET more suitable for another subgroup of patients with PD?

We still believe that strategic executive training could be a beneficial treatment for a specific subgroup of patients with PD. This would concern younger patients with PD than those included in this study. Patients, who are in the early stage of disease with only mild symptoms (H&Y I) and who are still actively participating within the domains of work, social relations, leisure activities and mobility. Strategy treatment would be an option if patients experience some burden of their impairments in EF which will fuel their motivation to undergo intensive treatment. Such a subgroup would probably be more comparable in terms of demographic characteristics to the ABI group in the study of Spikman et al. (2010), for whom strategic executive training was clearly beneficial.

Furthermore, we believe that it might be even best to offer patients with PD strategic executive training as soon as they report complaints of executive impairments in daily life, without having objective impairments, which was an inclusion criterion in our study. The main reason for this is that in the early stage of PD patients' memory capacity and attentional functions are largely intact which are essential requirements for learning new strategies and usually worsen when the disease progresses. Given that patients with PD will develop executive impairments somewhere along the course of their disease, it might be advantageous to already learn patients effective strategies during the early stages of the disease. Possibly, patients benefit longer from using such strategies by the time executive impairments worsen. Subjective impairments will probably better motivate patients to start an intensive intervention like ReSET, as compared to objective impairments, not (yet) experienced as burdensome in everyday life. Furthermore, we would highly recommend to actively involving partners or relatives during the treatment programmes in future research. When partners or relatives also become familiar with the tools and approaches that allow them to compensate for executive impairments early-on, it will probably lead to increased understanding of executive impairments.

They can use these methods to provide patients with more structure in later stages of the disease when patients become increasingly dependent of external structure and remind patients to make use of those strategies

Increasing patients' awareness of problems with time management and offering strategies to improve this seems to be particularly valuable when evaluating the treatment goals of patients with PD and the clinical experiences of working with the ReSET protocol. So, one could argue that giving patients and their partners or relatives psychoeducation on this topic might already be of significant value for improving their perceived impairments with EF in everyday life. This is an important issue to address in future studies, since it might provide a cost-effective treatment alternative for impairments in EF in patients with PD.

## Recommendations for neuropsychological assessment of EF in PD

In several studies as described in this thesis, evidence was found that impairments in EF are common in patients with PD. However, the clinical presentation of these impairments and the impact on everyday life seems to be different from ABI patients. To be able to use this knowledge in clinical practice, it is essential to know how problems with EF can be recognized in patients with PD. Or in other words: what is needed in neuropsychological assessment for patients with PD to get a realistic view on their specific impairments in EF?

Standard neuropsychological tests (e.g. Trail Making Test or a simple reaction time task (Vienna test system)) need to be administered in order to investigate whether patients show basal cognitive impairments they need to compensate for, such as attentional deficits, slowed speed of information processing or impairments in basal aspects of EF. In addition, neuropsychological tests for EF that are more complex and having a higher ecological validity (i.e. resembles the use of EF in everyday life to a greater extent) are essential to determine which impairments in higher-order EF form a problem in everyday life. Neuropsychological tests that provide patients with relatively little structure and do not involve high time pressure are suitable to use for this purpose. The Behavioural Assessment of the Dysexecutive Syndrome (Wilson et al., 1996) is a good example of such a test battery.

In order to get a more comprehensive view of related restrictions in everyday life in terms of complaints and performance, it is essential to add subjective measures (Chapter 3). Neuropsychological tests assess patients' optimal performance, whereas subjective measures such as questionnaires ask for patients' experienced burden of impairments in EF and offer the possibility to ask for those aspects of EF that are difficult to measure quantitatively such as initiative. To select patients for treatment subjective rather than objective measures will be helpful. Many patients with

complaints do not necessarily show impairments on the respective tests but experience some burden that motivates them for seeking support. Subjective questionnaires, such as the DEX questionnaire, that assess whether patients or relatives already report complaints about EF in everyday life are more important to include patients than impairment based on low scores on tests. In line with previous studies, we found no indications for an impaired self-awareness and thus PD patients' self-report on subjective measures must be considered as reliable.

A clinical interview with patients and their partners or relatives forms also an essential subjective element within the diagnostic process of impairments of EF. Assuming that loss of initiative is probably the core feature of impairment in EF, it is important to explicitly ask patients and their relatives if and how they perceive problems with this in everyday life. Subsequently, information can be derived on the severity of this initiative problem. For instance, one can ask if patients are still able to make a feasible day planning or whether they frequently experience a lack of time in everyday life situations. Relevant questions for relatives are whether they experience that patients have difficulty starting activities in the first place and whether they have to provide the patient with external structure (i.e. give clear instructions) to actually get activities done. We believe that the more patients depend in everyday life activities on external structure as provided by relatives, the more severe their initiative problem. In turn, this gives valuable information about what would be realistic goals for treatment and can even determine what kind of cognitive treatment programme (i.e. skills training versus strategy training) would be most beneficial.

With regard to the decision process of what kind of treatment would be most beneficial for patients with PD, it is also important to take patients' individual executive goals into account. Individual goals can be seen as a reflection of what would contribute to patients' participation and QoL. When someone is still actively participating in societal domains (e.g. work) and able to learn and use strategies, then a goal can be to fulfill the societal roles as long as possible. However, a more severely affected patient who needs already a lot of external structure would be pleased when, given his or her increased dependency, he or she would be able to perform a few specific everyday life activities independently. In the first example strategy training would be preferred, whether in the second example skills training might be a better option.

## Conclusions and future perspectives

We are convinced that in clinical practice objective (neuropsychological tests) and subjective measures (questionnaires and the clinical interview) have mutual added value when determining whether and to what extent patients with PD show and experience impairments in EF. Disease severity, current level of participation in

societal domains and the presence and severity of initiative problems (as core aspect of EF in PD) are considered crucial factors for determining what kind of cognitive treatment for impairments in EF is most likely to be successful for the individual patient. We suggest to provide strategy training for relatively young (<60 years) patients in the early stages of PD (or even the novo patients) who are still actively participating in societal domains and already report complaints about impairments in EF, without the necessity of objective impairments in EF. Older patients with a mild to severe disease severity who show evident initiation problems and a low level of societal participation might benefit from skills training only. Older patients with a mild disease severity and mild initiation problems who are not actively participating in societal domains (such as the patient group in this study) may benefit from strategy training or function training in terms of improving their self-efficacy.

This study is the first evaluating strategy treatment for EF deficits in PD and can be considered as pioneer work within the broad field of neuropsychological rehabilitation in neurodegenerative diseases. Our main finding was that patients with PD may benefit from neuropsychological treatment, either strategy or function training. Hence, the important message is that cognitive rehabilitation should be considered as a valuable treatment option for patients with PD despite the progressive course of the disease. Future research is needed to optimize the selection criteria for patients with PD most likely benefiting from cognitive rehabilitation. E-health solutions very likely will improve the availability of cognitive training programmes and lower the threshold to participate. Participation of spouses or relatives in the cognitive treatments should be considered as a pivotal ingredient of these therapies. Teaching relatives will provide optimal external structure, especially if patients start to show more EF dysfunction during the course of their disease. Future treatment programmes will also benefit from collaboration between all disciplines involved in health care for patients with PD, like (neuro)psychologists, physiotherapists and occupational therapists) (Sturkenboom et al., 2014). In conclusion, the main goal of an effective intervention should be to maintain the current level of cognitive functioning as long as possible.

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# Nederlandse samenvatting

## Ziekte van Parkinson

De idiopathische ziekte van Parkinson (ZvP) is na de ziekte van Alzheimer de meest voorkomende neurodegeneratieve ziekte. Het klinische beeld van de ZvP kenmerkt zich door motorische symptomen, zoals bradykinesie (traagheid en verminderde amplitude van bewegen), akinesie (bewegingsarmoede), rusttremor, rigiditeit en houdingsinstabiliteit. Voorts kunnen er zich een variëteit aan niet-motorische symptomen voordoen, zoals cognitieve stoornissen, neuropsychiatrische stoornissen (bijv. stemmingsstoornissen en hallucinaties), autonome disfuncties (bijv. orthostatische hypotensie), slaapstoornissen en vermoeidheid. Deze niet-motorische symptomen kunnen het zelfstandig functioneren van patiënten sterk belemmeren, evenals hun relatie met naasten. De Parkinsonistische symptomen worden hoofdzakelijk veroorzaakt door een progressieve degeneratie van dopamine producerende neuronen in de substantia nigra en ventrale tegmentum, welke onderdeel uitmaken van de basale ganglia. Daarnaast spelen veranderingen in noradrenerge, serotonerge en cholinerge transmittersystemen ook een rol in de etiologie van de de ZvP. De substantia nigra en ventrale tegmentum maken deel uit van de frontostriatale netwerken, waarin dopamine onmisbaar is. Binnen deze netwerken kan men een scheiding aanbrengen tussen het sensomotorische netwerk dat vooral van belang is voor motorisch functioneren, het associatieve-cognitieve netwerk dat betrokken is bij cognitieve en executieve functies en het limbische netwerk dat betrokken is bij het reguleren van emoties en besluitvorming. Wanneer bij patiënten met de ZvP de dopamineproductie afneemt zal dit dus niet alleen resulteren in problemen op het gebied van motorisch functioneren, maar ook op het gebied van cognitief functioneren en gedrag. Hierbij is de cognitieve achteruitgang het grootst wanneer er in het brein behalve een afname van dopamine, ook sprake is van een niet optimaal functionerend cholinerg systeem.

## Cognitieve stoornissen bij patiënten met de ZvP

Bij 25% van de patiënten met de ZvP is sprake van milde cognitieve stoornissen, die vaker voorkomen naarmate het ziekteproces vordert. Aan de definitie van milde cognitieve stoornissen (MCI) wordt volgens de Movement Disorders Task Force voldaan als er sprake is van 1) een geleidelijke verslechtering van cognitief functioneren, zoals gerapporteerd door de patiënt, naaste of behandelaar, 2) objectieve cognitieve stoornissen zoals gemeten met neuropsychologische testen of screeninginstrumenten voor algemeen cognitief functioneren en 3) wanneer de stoornissen niet substantieel interfereren met het dagelijks functioneren. Verder wordt er een onderscheid gemaakt tussen MCI waarbij er stoornissen geobjectiveerd worden in een of meerdere cognitieve domeinen (“single versus multiple domain”) en

tussen types waarbij er al dan niet sprake is van geheugenstoornissen ("amnestic versus non-amnestic"). Uit onderzoek blijkt dat niet-amnestische MCI vaker voorkomt dan amnestische MCI binnen de groep patiënten met de ZVP, waarbij stoornissen in executieve functies (EF) het meest voorkomen.

## Executieve functies

Zoals beschreven komen cognitieve stoornissen en in het bijzonder stoornissen in de executieve stoornissen vaak voor bij patiënten met de ZvP vanwege toenemend disfunctioneren van dopaminerge frontostriatale netwerken in het brein. Executieve stoornissen kunnen zich al manifesteren in de beginfases van de ziekte en worden soms al vastgesteld op het moment van diagnose.

EF zijn hogere orde functies die ons in staat stellen om doelgericht te handelen, realistische doelen te stellen en ons gedrag aan te passen aan veranderende omstandigheden. Vooral in nieuwe, niet-routinematige en complexe situaties wordt er een beroep gedaan op EF. In dit proefschrift worden EF als volgt gedefinieerd: *zelfinzicht, het kunnen stellen van realistische en concrete doelen, planning van benodigde deelstappen, initiatiefname, het monitoren van eigen gedrag, het kunnen inhiberen van gedrag dat niet tot het doel leidt, flexibiliteit en strategisch gedrag* ofwel het kunnen generaliseren van succesvol gedrag naar andere, soortgelijke situaties.

## Diagnostiek van executieve functies

Neuropsychologische tests worden veelal gebruikt voor het objectiveren van stoornissen in EF. Deze tests worden afgenomen in een gestandaardiseerde setting, waarbij mogelijke bronnen van externe afleiding worden geminimaliseerd. Dit bemoeilijkt echter het in kaart brengen van EF, omdat er op deze functies juist een beroep wordt gedaan in nieuwe, niet-routinematige, complexe en ongestructureerde situaties. De ecologische validiteit van standaard neuropsychologische taken (bijv. Trailmaking Test en Stroop Kleur-Woord test) wordt daarom laag geschat. Het gebruik van de testbatterij Behavioural Assessment of the Dysexecutive Syndrome (BADS) wordt daarentegen vanwege een hogere ecologische validiteit aangeraden. Vragenlijstonderzoek is een andere, meer subjectieve methode om EF in kaart te brengen. Middels vragenlijsten (bijv. Dysexecutive syndrome vragenlijst - DEX) kan men de mate en ernst bepalen waarin patiënten en hun naasten executieve stoornissen bemerken in het dagelijks leven. Mogelijk wordt op deze manier een meer realistische kijk verkregen op executieve problemen dan middels afname van neuropsychologische tests, omdat de lijsten rechtstreeks vragen naar de beleving van deze problemen in het dagelijks functioneren.

## EF en de relatie met dagelijks functioneren en kwaliteit van leven

Uit onderzoek is bekend dat er verscheidene executieve stoornissen voor kunnen komen bij patiënten met de ZvP. Problemen met het bewust sturen van de aandacht, flexibiliteit, planning, inhibitievermogen, probleemoplossend vermogen, multitasken, besluitvormingsprocessen en sociale cognitie worden het meest beschreven. Het zijn juist deze functies die essentieel zijn om dagelijkse activiteiten te kunnen plannen, organiseren en uit te voeren. Het zelfstandig functioneren van patiënten met de ZvP die eveneens kampen met stoornissen in EF wordt daardoor ernstig belemmerd en heeft een lagere kwaliteit van leven tot gevolg.

## Neuropsychologische behandeling

De Wereldgezondheidsorganisatie stelt in haar ICF (International Classification of Functioning) model dat een ziekte het functioneren van een patiënt op verschillende niveaus beïnvloedt: op functieniveau, activiteitenniveau en participatieniveau. Neuropsychologische behandeling helpt patiënten om te gaan met de cognitieve, emotionele, sociale en gedragsmatige gevolgen van (niet-aangeboren) hersenletsel en waar mogelijk deze gevolgen in te perken. Cognitieve revalidatie is onderdeel van neuropsychologische behandeling en bestaat doorgaans uit psycho-educatie, het maken van aanpassingen in de leefomgeving van een patiënt en cognitieve training. Cognitieve training onderscheidt trainingen op drie niveaus: functietraining (middels herhaalde oefening van taken trachten onderliggende functies te verbeteren), vaardigheidstraining (herhaalde oefening van specifieke dagelijkse taken met als doel de uitvoer van deze specifieke taken te verbeteren) en strategietraining (gebruik maken van intacte cognitieve functies om strategieën ter compensatie van cognitieve stoornissen aan te leren). Strategietraining overstijgt het niveau van functie- en vaardigheidstraining en richt zich van alle typen training het meest op het verbeteren van het participatieniveau. In recente literatuur wordt voornamelijk strategietraining effectief bevonden en aanbevolen als behandeloptie voor patiënten met niet-aangeboren hersenletsel en executieve stoornissen. Voor patiënten met de ZvP maakt cognitieve revalidatie echter nog geen deel uit van de standaard behandelopties, terwijl zij eveneens worden gehinderd door executieve stoornissen in het dagelijks leven.

In het proefschrift dat voor u ligt staan twee hoofdvragen centraal. De eerste vraag is diagnostisch van aard: in een groep patiënten met de ZvP wordt onderzocht welke stoornissen in EF kenmerkend zijn, op welke manier diagnostiek ingezet kan worden om deze stoornissen in kaart te brengen en hoe deze stoornissen interfereren in het dagelijks functioneren. Hierbij werd de hypothese gesteld dat de aard van de

stoornissen in EF gelijkenis toont met apathie en deels verklaard kan worden door onderliggende traagheid van informatieverwerking bij motorische en cognitieve processen. De tweede vraag richt zich op behandeling van executieve stoornissen: kan cognitieve behandeling tot verbetering leiden ten aanzien van executieve stoornissen in het dagelijks leven voor patiënten met de ZvP. Hierbij wordt verwacht dat een cognitieve behandeling bestaande uit strategische training (ReSET) effectiever is dan een behandeling gericht op training van specifieke cognitieve functies (Cogniplus).

Het primaire doel van de studie zoals beschreven in **hoofdstuk 2** was om te onderzoeken of mentale traagheid (bradyfrenie) onderscheiden kan worden van motorische traagheid (bradykinesie) bij patiënten met de ZvP. Met het begrip bradykinesie wordt in deze studie specifiek de traagheid van bewegen bedoeld (en niet: verminderde amplitude). Deze vraag werd onderzocht met gebruik van een eenvoudige reactietijdentaak (Vienna Test Systeem), waarbij de respons gescheiden werd in een mentale component (reactietijd) en een motorische component (motorische tijd). Indien mentale traagheid werd geobjectiveerd, was een tweede vraag in hoeverre mentale traagheid bij patiënten met de ZvP een voorspeller is van de prestaties op neuropsychologische tests. Verrassend genoeg werden er geen significante verschillen gevonden tussen de motorische tijden van patiënten en gezonde controles. De reactietijden van patiënten waren wel significant trager dan die van de gezonde controles. Op basis van deze uitkomsten concludeerden we dat patiënten met de ZvP behalve motorische traagheid inderdaad mentale traagheid kunnen vertonen. Verder bleek dat binnen de patiëntengroep reactie- en motorische tijden niet correleerden met klinisch maten van ziekte-ernst (H&Y en UPDRS-III). Mentale traagheid vormde geen voorspeller voor patiënten hun prestaties op neuropsychologische tests. De motorische tijden waren wel een voorspeller voor de prestatie op twee aandachtstests (TMT A en Stroop Kleur-Woord/Kleurkaart ratio). Dit impliceert dat er voor Parkinsonpatiënten bij de interpretatie van resultaten op deze tests rekening gehouden dient te worden met eventuele motorische traagheid, omdat dit de resultaten kan vertroebelen.

In **hoofdstuk 3** werd onderzocht in een groep niet dementerende patiënten met de ZvP of er een relatie bestaat tussen de uitkomsten van objectieve maten voor EF (neuropsychologische tests) en de uitkomsten van subjectieve maten (vragenlijsten) voor EF. Daarnaast werd onderzocht of executieve stoornissen (gemeten met objectieve dan wel subjectieve maten) een voorspeller zijn voor het niveau van participatie en de kwaliteit van leven van patiënten met de ZvP. De resultaten lieten zien dat er geen significante correlaties gevonden werden tussen uitkomsten van objectieve en subjectieve maten voor EF. Hieruit concludeerden we dat beide typen maten informatie verschaffen vanuit een ander perspectief en elkaar aanvullen. Bovendien leveren beide typen maten een unieke bijdrage aan het voorspellen van het participatieniveau en de kwaliteit van leven van patiënten met de

ZvP. Daarnaast kwamen sekse en ernst van de ziekte als matige voorspellers naar voren.

In **hoofdstuk 4** werd onderzocht of er legitieme redenen zijn om strategietraining niet als standaard behandeloptie aan te bieden voor patiënten met de ZvP met executieve stoornissen. Allereerst werd onderzocht of patiënten met de ZvP verschillen van patiënten met niet-aangeboren hersenletsel (NAH) in termen van hun cognitieve en executieve profiel (prestatie op neuropsychologische tests) en in termen van hun behoeften en vragen voor behandeling gericht op executieve stoornissen (individuele behandeldoelen). Beiden groepen ondergingen een uitgebreid neuropsychologisch onderzoek. Daarnaast werden patiënten hun doelen geclassificeerd in domeinen van EF en erna in domeinen van algemeen dagelijks functioneren en participatie. Uit de resultaten komt naar voren dat de patiëntengroepen een vergelijkbaar cognitief en executief profiel laten zien en vergelijkbare doelen stellen. Patiënten met de ZvP stelden meer doelen gerelateerd aan “time management” (aspect van EF) en “huishouden en tuinieren” (domeinen dagelijks functioneren) dan patiënten met NAH. Verder waren er geen significante verschillen tussen beide groepen. Concluderend, werden er geen argumenten gevonden voor de aanname dat patiënten met de ZvP niet kunnen profiteren van strategietraining voor executieve stoornissen.

**Hoofdstuk 5** beschrijft een review over cognitieve revalidatie bij patiënten met de ZvP. Er werden negen studies geschikt bevonden om te includeren, die in de periode 2004 tot en met 2013 zijn uitgevoerd. In het bijzonder is er aandacht besteed aan de mate waarin de onderzochte cognitieve behandelingen zich richtten op het verbeteren van EF, aangezien deze executieve stoornissen bij de ZvP op de voorgrond staan. De afzonderlijke studies zijn beoordeeld op basis van methodologische kwaliteit en effectiviteit. Daarnaast werden de cognitieve behandelingen geclassificeerd op basis van het type training dat centraal stond in de behandeling (functietraining, vaardigheids- en/of strategietraining). Ook de uitkomstmaten werden gecategoriseerd in drie categorieën, gebaseerd op het ICF model: maten op functieniveau, activiteiten/participatieniveau en maten gerelateerd aan persoonlijke factoren. Uit de resultaten blijkt dat de meerderheid van de studies van goede methodologische kwaliteit is en dat de beschreven behandelingen leiden tot een verbetering van het cognitief functioneren in termen van een verbeterde prestatie op neuropsychologische tests (functieniveau). Echter, zowel de behandelingen als de uitkomstmaten beperken zich in de meeste studies tot meten op functieniveau. Er is daarom nog onvoldoende inzicht in de mate waarin de gevonden effecten generaliseren naar het dagelijks functioneren. Voorts werd er relatief weinig specifieke aandacht gericht op het verbeteren van EF (in het dagelijks leven). Omdat strategietraining voor executieve stoornissen effectief is gebleken voor patiënten met NAH, stellen we dat toekomstig onderzoek nodig is om uit te zoeken in hoeverre

strategietraining ook effectief is voor het verbeteren van executief functioneren in het dagelijks leven, participatie in maatschappelijke domeinen en de kwaliteit van leven van patiënten met de ZvP.

**Hoofdstuk 6** beschrijft de resultaten van een RCT naar de effectiviteit van ReSET; a Strategic Executive Treatment (strategietraining) in vergelijking met een gecomputeriseerde functietraining (Cogniplus) bij een groep patiënten met de ZvP. Twee weken (nameting) en drie tot vijf maanden (follow-up) na de behandeling, rapporteerden patiënten in beide groepen een vooruitgang in de gestelde doelen en rapporteerden ze minder klachten omtrent executief functioneren in het dagelijks leven. Alleen ten tijde van de nameting was deze subjectief ervaren vooruitgang significant groter in de ReSET groep dan voor de patiënten in de Cogniplus groep. De naasten van patiënten in beide groepen rapporteerden na de behandeling echter niet een ervaren afname van de executieve problemen in het dagelijks functioneren van de patiënt. Daarom werd gesteld dat de gerapporteerde vooruitgang van patiënten geïnterpreteerd zou kunnen worden als een toename van *self-efficacy* (vertrouwen dat iemand heeft in zijn/haar vermogen om specifiek gedag uit te voeren), dat blijkbaar voor diens naasten niet concreet observeerbaar was in het dagelijks functioneren. Zowel ReSET als Cogniplus brachten geen veranderingen teweeg op participatieniveau en in de kwaliteit van leven. Dit betekent dat, in tegenstelling tot voor patiënten met NAH, er onvoldoende bewijs werd gevonden voor de hypothese dat strategietraining effectiever is dan functietraining voor het verbeteren van executief functioneren in het dagelijks leven, participatieniveau en de kwaliteit van leven van patiënten met de ZvP. Voor toekomstig onderzoek is het van belang om meer inzicht te krijgen in welke subgroep van patiënten met de ZvP en executieve stoornissen het meest profiteert van welk type behandeling, in termen van verbetering in het dagelijks functioneren en de kwaliteit van leven.

Dit proefschrift besluit met een algemene discussie in **hoofdstuk 7**, waarin de nadruk ligt op de implicaties van onze studies voor de klinische praktijk. Voorts worden er aanbevelingen beschreven voor toekomstig onderzoek, gebaseerd op de klinische inzichten die wij verkregen hebben tijdens de uitvoering van de studies zoals beschreven in de afzonderlijke hoofdstukken.

# Dankwoord

# Dankwoord

Jarenlang heb ik uitgekeken naar het moment waarop ik mijn dankwoord mocht gaan schrijven, om precies te zijn acht jaren lang. Acht jaren staan gelijk aan de duur van een basisschoolperiode, twee wetenschappelijke studies, twee termijnen van een Amerikaanse president, vier Olympische spelen en acht keer de vier seizoenen. Voor mij waren het acht jaren met vele persoonlijke hoogtepunten, maar ook met moeilijke periodes. Tijd om deze periode af te sluiten, maar niet alvorens een heel aantal mensen in mijn omgeving te bedanken zonder wie ik niet op dit punt zou zijn aanbeland.

Beste Joke, in de eerste plaats ben jij vanaf het begin mijn begeleider geweest, maar gaandeweg de jaren is onze band steeds hechter geworden. Het laatste jaar ging dan wel gepaard met tegenslag, maar het was waardevol om te ervaren hoe steunend we voor elkaar konden zijn. Ik wil je bedanken voor het vertrouwen dat je altijd in mij hebt gehouden en hebt getoond! Fijn was het dat ik te allen tijden bij je binnen kon lopen voor vragen en daarnaast natuurlijk ook dank voor jouw kritische wetenschappelijke blik op mijn stukken en kennis van de neuropsychologie, waar ik veel van heb geleerd. Daarnaast heb ik het altijd bewonderd dat je naast het gezinsleven een succesvolle carrière hebt, die er tijdens mijn traject toe leidde dat je van begeleider promoveerde naar promotor. Hopelijk houden we nog lang contact!

Leden van de leescommissie: prof. dr. M.A.J. de Koning-Tijssen, prof. dr. B.A. Schmand en prof. dr. C.M. van Heugten, hartelijk dank voor het lezen en beoordelen van mijn proefschrift.

Annelien en Hilde, ik wil jullie bedanken voor alle tijd die jullie hebben geïnvesteerd in het werven en behandelen van patiënten met de ziekte van Parkinson van het noorden tot zuiden des lands. Waar ik jarenlang vijf dagen per week aandacht kon geven aan dit onderzoek, moesten jullie het combineren met alle andere klinische werkzaamheden, onderwijs- en andere onderzoekstaken. Ik heb me beseft dat dit voor jullie een lastige taak was. Annelien, dank dat je uit het zuiden afreisde om mij bij te staan tijdens de moeilijkste anderhalf uur van de afgelopen acht jaren. Dat waardeerde ik zeer. Meriam den Ouden en Marly Strijkers, dank voor het neuropsychologisch onderzoek dat jullie in het kader van mijn onderzoek hebben verricht in Drachten en Maastricht.

Teus, met jouw volle agenda was het een uitdaging om daar een gaatje in te vinden. Ik heb soms letterlijk voor je deur staan posten, maar de momenten dat je kon overleggen waren altijd van toegevoegde waarde. Met jouw jarenlange klinische- en onderzoekservaring op het gebied van de ziekte van Parkinson wist je vaak een andere invalshoek te belichten, maar ook had je aandacht voor talige details. Voorts wil ik graag mijn waardering uitspreken voor jouw morele steun en vertrouwen het afgelopen jaar. Tot slot wil ik je bedanken voor het (samen met Martje Drent) werven van patiënten op de afdeling neurologie in het UMCG. En natuurlijk voor het feit dat je de rol als promotor op je hebt willen nemen.

Harriët Smeding, in de beginfase van het onderzoek ben je betrokken geweest om het behandelprotocol vorm te geven. Bedankt voor je klinische blik en ideeën.

Het meest belangrijk om te bedanken zijn de patiënten met de ziekte van Parkinson die bereid waren om deel te nemen aan mijn behandelstudie. Zonder hen zou er nu geen proefschrift liggen en was het mij niet gelukt om mijn motivatie tot het einde te behouden. Met bewondering heb ik al hun persoonlijke verhalen, maar ook die van partners en soms andere familieleden aangehoord over wat voor impact de ziekte van Parkinson heeft op het alledaagse leven in al zijn facetten. Veel moed, doorzettingsvermogen en optimisme is nodig van patiënten en naasten om het leven kleur te blijven geven als je (of je naaste) lijdt aan een ziekte die je zelfstandigheid stukje bij beetje inbindt. Bedankt voor al jullie openheid en inzet. Partners en familieleden, bedankt dat jullie bereid waren om patiënten naar het ziekenhuis te brengen voor behandelsessies en testdagen.

Ik wil de Parkinson vereniging graag bedanken voor het verstrekken van een subsidie, waarmee reiskosten konden worden vergoed voor patiënten die deel namen aan de studie.

In 2014 heb ik me een periode mogen aansluiten als vrijwilliger bij het Parkinson café in Groningen, waar patiënten en hun naasten bijeen komen om informatie te krijgen van hulpverleners, maar vooral voor het lotgenotencontact en deelname aan sociale activiteiten. Miranda van Beveren, Thea de Haan, Vally Hardenberg en Greetje Teuben, jullie bevlogenheid en betrokkenheid bij deze doelgroep was zeer bewonderenswaardig om van dichtbij mee te maken. Ik vond het heel mooi om te zien hoe jullie, naast je rol als hulpverlener, ook als mens een steentje bijdroegen aan het welbevinden van patiënten en hun omgeving. Het was voor mij een leerzame ervaring om bij jullie te mogen aansluiten en bovenal ongedwongen gezellig!

Tijdens het onderzoek had ik ook niet zonder de hulp van verscheidene psychologiestudenten gekund, die verantwoordelijk waren voor het afnemen van neuropsychologische tests en vragenlijsten bij patiënten en gezonde proefpersonen. Inmiddels zullen jullie allen zelf al enige tijd werkzaam zijn als psycholoog, maar Brenda Goldhoorn, Loes Keur, Tessa Jansen, Anneroos Dekker, Lars Röben, Iris Bergman, Diniek Kanis, Annemarie Slim, Annemiek Breshamer en Ruben Bakker bedankt!

De eerste helft van mijn promotietraject maakte ik actief deel uit van de vakgroep Clinical and Developmental neuropsychology van de faculteit Gedrags- en Maatschappijwetenschappen aan de Rijksuniversiteit Groningen. In het bijzonder wil ik de secretaresses Josje de Roo en Jolanda Polling bedanken voor de ondersteunende taken die zij hebben verricht gedurende mijn onderzoek. Verder wil ik José Heesink, Kees Aarts en Anke Bouma, dank voor jullie luisterend oor en steun in verschillende vormen.

Mijn onderzoek werd mede gefinancierd door het Nationaal Initiatief Hersenen en Cognitie (NIHC) van NWO en maakte in dat kader deel uit van het landelijke consortium cognitieve revalidatie. In het bijzonder wil ik Carolien van Heugten bedanken als projectleider van het consortium. Ieke, Hileen, Marieke en Dirk, het contact met jullie als medeonderzoekers heb ik al die jaren erg waardevol gevonden. Niet alleen voor een stukje lotgenotencontact, maar vooral vanwege de gezellige borrels, etentjes en congressen waar we over onze persoonlijke levens bijkletsten. In de periode dat jullie de onderzoeken afrondden, liet mijn promotiefeest nog op zich wachten. Ik zette daar wel een trouwfeest tegenover waar jullie goed vertegenwoordigd waren. Super leuk dat jullie toen naar Ezinge in het hoge noorden zijn afgereisd!

De meeste uren in ruim vier jaar heb ik zitten zwoegen in kamer 214 van het UMCG, maar gelukkig niet alleen. Mandy, Gera en Marjon, jullie hebben mij vanaf het eerste uur vergezeld. Mandy: OFF, do you still know me? ;). Thanks for all the moments of laughter and for your sarcasm, which put all our serious research stuff in perspective. Gera, goede herinneringen heb ik aan het congres in Bergen waar wij samen met Marjon een kamer deelden. Die 10 artikelen waar we het geregeld over hadden heb jij inmiddels ook echt geschreven. Marjon, wij zijn tot op de dag van vandaag partners in crime. Wat hebben we veel met elkaar gedeeld, niet alleen zaten we in hetzelfde schuitje dat RCT onderzoek heet, maar ook hebben we beide op persoonlijk vlak heel wat life events doorgemaakt. Waar we bij start van het onderzoek nog nagenoeg buren waren, zijn we inmiddels beiden verhuisd. We zijn beiden getrouwd. Jij kreeg

twee prachtige zoons en ook op dat vlak is de achtervolging ingezet. Het 10- jaren project waar we vaak grappend voor vreesden is het niet geworden, want ook voor jou staat de promotie op de planning. Dank voor alle inhoudelijke overlegmomenten en persoonlijke steun! Ons contact eindigt niet na de promoties; maar snel weer borrelen bij de Dame…of ergens anders ;). Buunk en Scheenen, jullie waren de tweede lichting kamergenootjes met wie ik in diezelfde kamer 214 zat. Jullie humor was een zeer prettige afleiding.

Lieve collega's van het MCL, sinds 2015 maak ik deel uit van de vakgroep Medische psychologie. Jullie hebben mij de gelegenheid gegeven om me verder te ontwikkelen als diagnosticus en behandelaar in de klinische praktijk. Zeker de afgelopen twee jaren waarin ik de kans kreeg om de GZ-opleiding te volgen. Mijn passie voor het vak is eigenlijk alleen maar toegenomen, door de prettige leeromgeving die jullie bieden, maar ook omdat ik me ontzettend tussen jullie thuis voel als persoon. Jullie steun afgelopen jaar was echt hartverwarmend en heeft me erg geholpen. Gerdien, Wytske en Jo-Anneke, ik wil jullie in het bijzonder bedanken voor jullie grote betrokkenheid, het aanhoren van mijn verhalen en bovenal de wijze levenslessen die ik van jullie heb geleerd. Ik hoop nog lang deel uit te maken van onze vakgroep!

Ik had het vooraf nooit zo kunnen bedenken, maar een dag na de promotie zal ik het theoretische deel van mijn GZ-opleiding afronden. Mede GéZetters, bedankt voor al jullie klinische ervaring waar ik veel van heb geleerd én alle keren dat jullie oprecht geïnteresseerd waren in hoe het stond met 'het onderzoek'. Linda, Rik, Linda S. en Zeljka, jullie lieve woorden (of unicorns en sterretjes Zeljka) op de juiste momenten hebben me heel goed gedaan, maar zeker ook de relativerende humor. Hopelijk houden we nog lang contact!

Henk Albert en Thea, Mirjam Esther en Gerard, Anne Femke en Twan: ook al zijn we door onze drukke levens niet vaak bij elkaar, onze band is er niet minder om. Ook jullie toonden afgelopen jaar allemaal op je eigen manier betrokkenheid, dankjewel! Anne Fem, jij in het bijzonder bedankt voor het maken van de prachtige kaft (ook al heeft dat zo'n 10 bossen tulpen gekost)! Jij hebt die creatieve genen waarvan ik er geen enkele bezit, geweldig. Jaap Jan en Betty, Annemiek en Sander, oma Mienie, Pieter en Jeanette, Gert, Johan en Wessel: bedankt voor die Blumen en jullie voelbare steun! Ik voel me volledig onderdeel van de familie, ook al ben ik Fries en van de ´koude kant´ (net als Pieter).

Leave heit en mem, doorzettingsvermogen, een sterk rechtvaardigheidsgevoel en eerlijkheid zijn eigenschappen die ik zonder twijfel van jullie heb meegekregen in het leven en zonder welke ik dit traject niet tot een goed einde had kunnen brengen. Ontzettend bedankt voor jullie onvoorwaardelijke steun, liefde en vertrouwen door de jaren heen. Vanaf nu is er weer één zorg minder.

Renske en Jelle, Marion en Gerard, Boukje & Maryam, Jan-Willem en Nelleke, Cor en Linda, Klaas en Marion, Chris en Cindy, Rudy en Marloes, Jochem en Hanna, Anton en Jacquelien, Femke: bedankt voor alle ontspannende momenten tijdens de afgelopen jaren. Daarmee doel ik op wijntjes drinken, Japanner-etentjes met Japannerkoek en vliegende eieren, alle andere niet-Japanse etentjes, Chris zijn culinaire bbq uitspattingen, festivals, concerten, pubquizzen, wandelingen etc. Laten we deze vriendschappen nog jaren in standhouden! Renske en Marion, heel fijn dat jullie mij op het moment suprême bij willen staan als paranimfen.

Dan rest er nog één iemand om te bedanken, aan wie ik minstens een pagina had kunnen wijden. Allerliefste Tjibbe, zo lang wij elkaar kennen ben ik bezig met dit promotieonderzoek. Jij bent het beste wat me in die jaren is overkomen en zonder jou was ik er zeker weten niet in geslaagd om het onderzoek af te ronden. Jij was er altijd voor me op de momenten dat het tegenzat. Mijn mentale veerkracht is door jouw onuitputtelijke positivisme en relativeringsvermogen exponentieel toegenomen door de jaren. Daarnaast was je mijn discussiepartner over inhoudelijke stof, vraagbaak over het maken van tabellen en Excel, mijn metgezel in het vieren van alle hoogtepunten (helaas de komende tijd geen publicatiedinertjes meer voor je) en data-entry medewerker haha. Ik ben je dankbaar voor de lay-out die er door jou zo netjes uit ziet. Ik hou van je en heb ontzettend veel zin om samen de nieuwe uitdaging in ons leven aan te gaan die over een paar maanden op ons wacht!

En dan is het nu tijd om een punt te zetten achter deze leerzame tijd. ●

# Curriculum Vitae

# Curriculum Vitae

In het kleine watersportdorp Heeg in Friesland werd Thialda Teakje Vlagsma geboren op 15 april 1987. Na haar Vwo-opleiding op Bogerman in Sneek, koos Thialda in 2005 voor de studie Psychologie aan de Rijksuniversiteit Groningen. Het studentenleven van Thialda was gevuld met gezelligheid, vrienden, sport, Grey's Anatomy en natuurlijk hard studeren voor de vele enerverende vakken die de studie Psychologie rijk was. Welke van deze factoren heeft geleid tot haar interesse in neuropsychologie is onduidelijk, maar het succesvol afronden van haar bacheloropleiding vloeide logischerwijs voort in een keuze voor de master Hersenen en Gedrag. Tijdens een klinische stage in 2009 in het UMCG gedurende deze master, maakte Thialda kennis met het doen van neuropsychologisch onderzoek bij diverse patiëntgroepen. In diezelfde periode voerde zij een onderzoeksproject uit bij jongvolwassenen die als kind waren behandeld voor een hersentumor naar de effecten van behandeling op arbeidsparticipatie en sociale cognitie. Ook werkte Thialda mee aan een normeringsonderzoek van de Nepsy-2. Een stageadres als het UMCG prikkelde haar leergierigheid en leidde tot een promotieplaats over cognitieve behandeling voor patiënten met de ziekte van Parkinson. Deze periode van promoveren bracht Thialda op vele bijzondere plekken. Presentaties over haar onderzoek werden gegeven op congressen in onder andere Finland, Oostenrijk, Zwitserland, Noorwegen en op Cyprus. Op laatstgenoemde twee locaties leidde dit zelfs tot indrukwekkende prijzen: een 'Highly recommended award' en een 'Best datablitz award'. Ook heeft Thialda zich tijdens haar promotie ingezet als vrijwilliger voor het Parkinson Café en voor de organisatie van een symposium voor de sectie Neuropsychologie van het NIP. Haar ervaring en expertise heeft ze vervolgens toegepast bij Revalidatie Friesland in Beetsterzwaag, waar ze patiënten met niet-aangeboren hersenletsel heeft behandeld. Sinds 2015 werkt Thialda als psycholoog in het Medisch Centrum Leeuwarden op de afdeling Medische Psychologie. Hier verricht zij diagnostiek en behandelt zij verscheidene interessante patiëntgroepen en heeft ze haar klinische ervaring verder verbreed, onder andere door middel van haar (bijna afgeronde) GZ-opleiding.

Als metgezel van Thialda gedurende haar lagere school, middelbare school en studieperiode kan ik met volle overtuiging stellen dat Thialda een perfecte gespreks- en samenwerkingspartner is. Ik ben ontzettend trots dat ik zo veel jaren naast haar heb mogen zitten in klaslokalen en collegezalen in het noorden des lands en natuurlijk op het feit dat ze met het afronden van dit proefschrift zichzelf doctor mag noemen.

Renske Zuurveen